Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

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The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from PTC Therapeutics Limited:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. AADC Research Trust
   b. Metabolic Support UK
   c. AADC Research Trust and Metabolic Support UK – patient case studies
      i. Case study 1
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4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

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Post-technical engagement documents

6. **Technical engagement response from** PTC Therapeutics Limited

7. **Technical engagement responses and statements from experts:**
   a. Simon Heales– clinical expert, nominated by AADC Research Trust
   b. Richard Poulin- clinical expert, nominated by Metabolic Support UK
   c. Professor Manju Kurian, NIHR Research Professor, UCL Professor of Neurogenetics, and Honorary Consultant in Paediatric Neurology – clinical expert, nominated by AADC

Research Trust

8. **Technical engagement responses from stakeholders:**
   a. AADC Research Trust
   b. NHS England

9. **External Assessment Report critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

10. **Company letter regarding updated PAS from** PTC Therapeutics

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Upstaza® (eladocagene exuparvovec) for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Document B

Company evidence submission

May 2022

File name	Version	Contains confidential information	Date
ID3791_eladocagene exuparvovec for AADC_HST_Company Evidence Submission_v1.0_17May2022_FINAL_ FullyRedacted	1.0	Yes	17 May 2022

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Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
AADC	Aromatic L-amino acid decarboxylase
AAV2	Adeno-associated virus serotype 2
AE	Adverse event
AIMS	Alberta Infant Motor Scale
BMJ	British Medical Journal
BSC	Best supportive care
CASP	Critical appraisal skills programme
CDITT	Comprehensive Developmental Inventory for Infants and Toddlers
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CI	Confidence interval
CI	Confidence interval
CNS	Central nervous system
CP	Cerebral palsy
CRD	Centre for Reviews and Dissemination
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
DCE	Discrete choice experiment
DDC	Dopa decarboxylase
DSU	Decision Support Unit
DTR	Deep tendon reflex
EEACT	Economic evaluation alongside clinical trials
EED	Economic evaluation database
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMBASE	Excerpta Medica database
FMT	Fluorescence molecular tomography
GMFM-88	Gross motor function measure
hAADC	Human aromatic L-amino acid decarboxylase
HCRU	Healthcare resource utilisation
HEOR	Health economic and outcomes research
HIAA	Hydroxy indoleacetic acid
HRQoL	Health related quality of life
HTA	Health technology assessment
HVA	Homovanillic acid
ICER	Incremental cost-effectiveness ratio
IEC	Independent Ethics Committee
iNTD	International Working Group on Neurotransmitter Related Disorders
IPD	Individual patient data
IRB	Institutional Review Board
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LCL	Lower confidence interval
L-DOPA	Levodopa
LL	Lower limit
LS	Least squares
MAO	Monoamine oxidase
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject heading
MHRA	Medicine and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NHDB	Natural history database
NHS	National Health Service

NICE	National Institute for Health and Clinical Excellence
OD	Optical density
OGC	Oculogyric crisis
OWSA	One way sensitivity analysis
PAS	Patient Access Scheme
PD	Pharmacodynamic
PDMS-2	Peabody Developmental Motor Scales Second Edition
PET	Positron emission tomography
pHC	Proportion of subjects achieving full head control
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Prescribed Specialist Services
pSS	Proportion of subjects able to stand with support
pSU	Proportion of subjects able to sit unassisted
pWA	Proportion of subjects able to walk with assistance
QALY	Quality-adjusted life year
QoL	Quality of life
rAAV2-hAADC	Recombinant adeno-associated virus vector encoding human cDNA of the DDC gene
RCT	Randomised control trial
SAE	Serious adverse event
SAP	Statistical analysis plan
ScHARRHUD	School of health and related research, University of Sheffield
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratios
TEAE	Treatment-emergent adverse event
TH	Tyrosine hydroxylase
TSD	Technical support document
UCL	Upper confidence interval
UK	United Kingdom
USA	United States of America
VG	Vector genomes
VTA	Ventral tegmental area
WHOQOL	World Health Organisation Quality of Life
WTP	Willingness to pay

Executive summary

Nature of the condition (Section B.1.3)

Aromatic L-amino acid decarboxylase (AADC) deficiency is an ultra-rare, genetic disorder, with a wide range of severe symptoms, and in severe cases, commonly results in patients being bedridden with little or no motor function couple with premature death within the first two decades of life.[1] It is characterised by a mutation in the *DDC* gene, which causes an absence of the AADC enzyme and in turn leads to severe deficiency of dopamine and other neurotransmitters essential for normal development, movement, learning, cognition, and autonomic function.[2]

AADC deficiency is extremely rare with an estimated birth rate of 1 in 118,000 births[3] in Europe. There are just 9 diagnosed patients in the UK,[4] equating to a UK prevalence of approximately 1 in 7.5 million people. Most patients (80%) with AADC deficiency present with a severe phenotype (early onset hypotonia, oculogyric crises [OGCs], dystonia, impaired development), defined by International consensus guidelines as no or very limited developmental milestones and full dependence.[2] Eladocagene exuparvovec is expected to be used in patients presenting with a severe phenotype, which UK clinical experts estimate to be [redacted] currently and [redacted] per year in subsequent years.[5]

Severe AADC deficiency is a life-shortening condition. While robust published estimates of AADC deficiency survival are limited, clinical experts and most studies report that patients with severe AADC deficiency die before their teenage years.[1,5–7]

In addition to being fatal, AADC deficiency places a profound and wide-ranging burden on affected children from birth onwards, affecting major aspects of their development, motor function, growth, cognitive and language skills, behaviour, and autonomic function.[3,6,2] The most common characteristic of severe AADC deficiency is lack of motor development, with over 95% of patients having very limited motor function and failing to achieve key motor milestones (i.e. bedridden or lacking the ability to sit independently) throughout their shortened lifetime.[6,8] Patients experience other motor impairments including hypotonia (low muscle tone/floppiness), dystonia (involuntary muscle contractions), and hypokinesia (smaller than expected movements).[9] The severe and devastating impact of AADC deficiency on motor function is highlighted in videos in Tai *et al.*, 2022 (please see video of a patient aged 2.5 years with severe AADC deficiency).[10]

In addition to failing to achieve key motor milestones, patients suffer a range of neurologic, autonomic, and cognitive impairments, including excessive crying, sleeping problems, irritability, problems with digestion, cognitive impairment, developmental delay, and autonomic symptoms.[9,2] A hallmark of AADC deficiency is frequent and painful episodes of seizure-like OGC during which the child's eyes roll upward without control and they experience tongue thrusting, jaw spasms, hyperextension of the head/neck/back, and involuntary muscle contractions.[9,2]

There are very limited published health-related quality-of-life (HRQoL) data in AADC deficiency due to the ultra-rare nature of the condition, the cognitive impairment and young

age of affected children. Studies reporting on QoL identify a wide range of symptoms that affect patient's quality-of-life (QoL), including having very limited or no motor function so being completely dependent on caregiver support, excessive crying, sleep disturbance, irritability, frustration, and inability to communicate or interact socially.[7,11,2] The QoL burden extends to caregivers who are required to provide round-the-clock care for their child with AADC deficiency.[11,12] Patients require support from at least 2 caregivers, who report providing 13 hours of practical and emotional care per day and a further 15 hours per week on administrative tasks.[13] Caregivers report a profound emotional burden, including depressive symptoms, sadness, anxiety, and impacts on their career, family relationships and social lives.[11,12]

There are currently no licensed treatments for AADC deficiency and no treatments that modify the disease course. Patients are currently managed with best supportive care (BSC), involving an extensive list of symptomatic treatments and management by a multi-disciplinary team of specialists.[14,2] The most commonly used treatments are those that target the dopamine pathway, including dopamine receptor agonists and monoamine oxidase (MAO) inhibitors.[2] However, some of these treatments, such as dopamine receptor agonists, are associated with side effects that hinder development, and they have not been observed to attenuate the progression of AADC deficiency.[15,2] Patients see a wide range of specialists as part of BSC, including paediatric neurologists, gastrointestinal specialists, endocrinologists, orthopaedic surgeons, speech therapists, pulmonologists, and physical and occupational therapists.[2] In the UK, there are very few specialist centres with experience of managing patients with AADC deficiency.

There is a clear and urgent unmet need for disease-modifying therapies that address the genetic root cause of AADC deficiency given that over 95% of patients with AADC deficiency do not achieve motor milestones during their lifetime despite the use of BSC.[8]

The technology: eladocagene exuparvovec (Section B.1.2)

Eladocagene exuparvovec (Upstaza®) will be the first and only licensed gene replacement therapy in AADC deficiency. It is indicated for the treatment of [redacted].[14]

Eladocagene exuparvovec is a single use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen (two infusions per putamen).[14] After infusion into the putamen, eladocagene exuparvovec results in the expression of the AADC enzyme and subsequent production of dopamine, in turn improving motor function in treated patients with AADC deficiency.[14] As a highly specialised technology, eladocagene exuparvovec is expected to be delivered at 1 or 2 specialist centres in the UK, where the technology and expertise to deliver the therapy and monitor patients already exists.

Clinical effectiveness (Section B.2)

Eladocagene exuparvovec has been studied in three single-arm Phase I/II clinical studies involving 28 patients with a confirmed diagnosis of severe AADC deficiency.[10,16–18] Given the rarity and severity of the condition, a comparator arm was not possible for ethical reasons. The primary endpoint in each study was proportion of patients achieving key motor milestones (full head control, sitting unsupported, walking with assistance, standing with support) as measured using a well-established measure of child motor development (Peabody Developmental Motor Scales Second Edition (PDMS-2)).[10,16–18] The primary endpoint timepoint was 60 months in two studies (AADC-010, AADC-CU/1601) and 12 months in one (AADC-011).[16–18] Studies were similar in terms of patient demographics, with a mean age at baseline of 4 years and a mean PDMS-2 score of 8.75–14.67, indicating no motor function.[10,16–18] UK clinical experts have validated that the patients in the studies are generalisable to those expected to be treated in the UK.[5]

Primary outcome: motor milestones

Eladocagene exuparvovec delivered rapid, clinically meaningful, and durable improvements in patient outcomes. Despite all 28 patients treated with the licensed dose having no motor function at baseline and expected to achieve no motor milestones during their lifetime (according to natural history data[8] and UK clinical experts[5]), patients treated with a single dose of eladocagene exuparvovec significantly improved in motor milestone achievement compared with baseline and improvements were durable, persisting for at least five years.[10,16–18] The transformative and life-changing benefits of eladocagene exuparvovec are demonstrated by patient videos in Tai *et al.*, 2022[10] (baseline: here; 5-year follow-up: here) and presented to the EMA Scientific Advisory Group, video of Patient 311.[19]

In AADC-010, all patients had no motor function at baseline and achieved the following motor milestones at key timepoints over a long-term follow-up of 60 months:[18]

- At month 12, [redacted] patient ([redacted]%) had full head control and [redacted] ([redacted]%) could sit unassisted.[18]
- At month 24, [redacted] patients ([redacted]%) had full head control, [redacted] ([redacted]%) could sit unassisted, and [redacted] ([redacted]%) could stand with support.[18]
- At Month 60 following a single dose of eladocagene exuparvovec, [redacted] patients achieved full head control ([redacted]%), [redacted] could sit unassisted ([redacted]%), [redacted] could stand with support ([redacted]%), and [redacted] could walk with assistance ([redacted]%).[18]

In AADC-011, all patients had no motor function at baseline. At the primary endpoint follow-up of 12 months:

- [redacted] of 9 patients ([redacted]%) with Month 12 data achieved full head control.[17]
- [redacted] of 9 patients ([redacted]%) with Month 12 data could sit unassisted.[17]

In AADC-CU/1601, all patients had no motor function at baseline and achieved the following motor milestones at key timepoints over a long-term follow-up of up to 10 years:[16]

- At month 12 following a single dose of eladocagene exuparvovec, [redacted] patients ([redacted]%) achieved full head control and [redacted] patients ([redacted]%) could sit unassisted.[16]

- At month 24, [redacted] patients ([redacted]%) had full head control and [redacted] ([redacted]%) could sit unassisted.[16]
- At month 60 following a single dose of eladocagene exuparvovec, [redacted] patients ([redacted]%) had full head control, [redacted] patients ([redacted]%) could sit unassisted, and [redacted] patients ([redacted]%) were able to stand with support.[16]
- Patients with 5–10 years of follow-up continue to show improved motor function compared with baseline.[10]

Secondary outcomes

Across all studies, patients treated with eladocagene exuparvovec experienced rapid and durable global symptoms improvements compared with baseline, including:

- Significant improvement in motor function, as measured by PDMS-2 score (P<0.0001 in all studies).[10,16–18]
- Significant improvement in development/motor function, as measured by the Alberta Infant Motor Scale (P<0.0001 in all studies).[10,16–18]
- Significant improvement in development and cognition, as measured by the Comprehensive Developmental Inventory for Infants and Toddlers in AADC-CU/1601 (P<0.0001)[16] and the Bayley-III scale in AADC-010 (P<0.0001)[18] and AADC-011 (P<0.0001).[17]
- Reduced frequency of OGC and proportion of time spent experiencing OGC episodes.[16–18]
- Reduced frequency of floppiness, limb dystonia, stimulus-provoked dystonia, and OGC facial dyskinesia.[16–18]
- Significant increase in body weight (P<0.05 in all studies).[16–18]

Objective evidence of a functioning AADC enzyme was proven in all patients through an increase in levels of dopamine metabolites in the cerebrospinal fluid and putaminal-specific positron emission tomography (PET) uptake of F-DOPA.[16–18]

Quality-of-life

In a retrospective assessment of caregiver QoL and patient symptoms, of the 17 caregivers who returned the World Health Organization Quality-of-life (WHOQOL)-BREF survey, there were significant improvements (P<0.001) in all domains of caregiver QoL (overall health, physical health, psychological, social relationships, environment) compared with baseline.[10] Caregivers also reported significant improvements in patient symptom severity, including mood, sweating, temperature, and OGCs.[10]

Safety

In a pooled safety analysis of 28 patients treated with the licensed dose of eladocagene exuparvovec:[20]

- *Most of the common adverse events (AEs) were typical symptoms of AADC deficiency*: Of the [redacted] AEs across 28 patients in the three studies, common AEs included pyrexia,

dyskinesia, upper respiratory tract infection, gastroenteritis, pneumonia, upper gastrointestinal haemorrhage. At least 1 AE was reported by all patients.

- *AEs were mostly mild or moderate, and none were definitely treatment related*: [redacted] of the [redacted] AEs were severe, with [redacted] moderate AEs and [redacted] mild AEs. No AEs were considered definitely related to treatment and only [redacted] were considered possibly/likely related.

Comparative effectiveness

AADC deficiency is ultra-rare with no licensed therapies, meaning that there is a paucity of published evidence related to the disease and potential treatments. In addition, eladocagene exuparvovec was studied in single-arm trials due to the rarity of the condition and for ethical reasons.

The comparator in this submission is BSC, defined as symptomatic treatment and care by a multi-disciplinary team of specialists as part of established clinical management. Comparator clinical data in this submission are provided through a patient-level cohort based on a Natural History Database (NHDB) of all known cases of patients with AADC deficiency worldwide, as identified by systematic literature review (SLR).[8] The SLR identified 49 unique patients with sufficient data to indicate that they had a severe phenotype.[8] Of the 49 patients, 47 (96%) failed to achieve any motor milestones despite ≥5 years of follow-up in some patients.[8]

An indirect treatment comparison (ITC) using the eladocagene exuparvovec studies and the NHDB has been explored using the recommended methods in the Decision Support Unit's Technical Support Documents[21,22] for single-arm and observational data. While propensity score matching was the most suitable methodology, it was not feasible as the matching exercise vastly reduced the sample size of the population and created weights that varied widely between patients, indicating unstable matching. As such, a naïve comparison between eladocagene exuparvovec and BSC was conducted and showed that patients treated with eladocagene exuparvovec achieve substantial improvement in motor milestone achievement compared with baseline, whereas 96% of patients treated with BSC in the NHDB do not achieve any motor milestones.

Cost-effectiveness (Section B.3)

Methodology

A de novo cost-effectiveness analysis (CEA) was developed to investigate the cost-effectiveness of eladocagene exuparvovec versus BSC in terms of life years gained, quality-adjusted life-years (QALYs) gained, incremental costs, and incremental cost per QALYs gained. The model has a lifetime time horizon and an NHS and Personal Social Services perspective. A 1.5% discount rate on costs and QALYs was applied, in line with NICE HST guidance[23] for products that provide life-changing and sustained clinical benefits.

The CEA consists of two parts: a short-term developmental phase, where patients can achieve motor milestones, and a long-term extrapolation phase, where they remain in the same motor

milestone throughout their lives. This structure was discussed and validated by clinical and health economic and outcomes research (HEOR) experts.[5,25,26] Given the correlation between motor milestones and other AADC deficiency symptoms, the CEA assumes global symptom improvement (i.e. as motor function improves, other AADC deficiency symptoms improve), which has been validated by 7 clinical experts.[5,26]

Motor milestone achievement in patients treated with eladocagene exuparvovec is based on modelling of the observed individual-patient trial data. The development phase uses Bayesian modeling of observed trial data to predict PDMS-2 scores over time, followed by a cumulative ordered logit model to estimate motor milestones based on the predicted PDMS-2 scores. The BSC arm is based on data from the NHDB.

Due to the paucity of published data on survival in AADC deficiency patients, survival data in the CEA were provided by the most appropriate proxy identified by clinical experts – cerebral palsy (CP).[5,24,25] Survival estimates from CP were used as a proxy to map onto AADC deficiency motor milestone health states and extrapolated using standard parametric models. The choice of CP as a proxy has been validated by clinical experts in a number of consultations, including with clinical experts in the UK.[5,25,26]

Quality-of-life data in the CEA were derived from a UK vignette study in which utilities were elicited for the CEA motor milestone health states using time-trade off methodology.[27] The CEA includes caregiver disutilities sourced from a suitable proxy that involves motor dysfunction.[28,29] The CEA reflects the caregiver burden that reduces with improving motor milestone achievement.

The CEA considers costs related to the acquisition, administration, and monitoring of eladocagene exuparvovec, as well as costs related to disease management and adverse events. Costs were derived from standard sources (e.g. NHS Schedule of Reference Costs).

Results

In the base case analysis, eladocagene exuparvovec generates [redacted] additional life years and [redacted] additional QALYs compared with BSC. Patients accrue a significant, meaningful benefit after treatment with eladocagene exuparvovec, resulting in the relevance of the NICE HST QALY modifier to this appraisal. At the list price of eladocagene exuparvovec, the ICER versus BSC is £176,343. With a patient access scheme (PAS) discount of [redacted]% (net price: £[redacted]), the ICER vs BSC is £[redacted].

Given the very limited data available to support a CEA in AADC deficiency, sensitivity analyses highlight some uncertainty in the model. In a probabilistic sensitivity analysis (PSA) with 1000 simulations, the mean PSA results lie close to the deterministic base case results, indicating the model is robust to parameter uncertainty (mean ICER at list price: £[redacted] [95% CI: £[redacted], £[redacted]]). The one-way sensitivity analysis (OWSA) shows that the key model drivers are caregiver disutility for patients in the no motor function and full head control health states, and utility values in the standing with support, sitting unassisted, and no motor function health states. Scenario analyses show that the ICER is most sensitive to the QALY modifier

and discount rate on costs and QALYs. Scenarios demonstrate that the base case results are robust to changes in key model parameters (e.g. utilities, motor milestone modelling).

Budget impact (Section B.3.16)

A de novo budget impact model (BIM) was developed in line with the CEA and NICE guidance, with a 5-year time horizon and NHS and PSS perspective. It is expected that [redacted] in Year 1 and [redacted] new [redacted] in each year in Years 2–5 would be eligible for eladocagene exuparvovec.[5] For current management without the introduction of eladocagene exuparvovec, it is assumed that all patients are treated with BSC. Following the introduction of eladocagene exuparvovec, it is assumed that all patients are treated with the new therapy given the poor prognosis with BSC and lack of alternative, licensed treatment options.

With the PAS price, it is estimated that the net budget impact of eladocagene exuparvovec is £[redacted]–£[redacted] each year over 5 years.

Benefits not captured in the QALY calculation (Section B.3.13)

AADC deficiency is a very severe, life-shortening genetic condition in which most patients on BSC spend their whole lives with very little motor or cognitive function and die before their teenage years. A single dose of eladocagene exuparvovec offers transformative, life-changing and life-long benefits with some children able to run, learn, and talk after therapy (see Tai *et al.* 2022[10] video and the EMA Scientific Advisory Group video of Patient 311,[19] which shows children able to live a normal life following gene replacement therapy).

Given the transformative benefits, eladocagene exuparvovec is expected to allow patients to pursue education and caregivers to increase work productivity. It is also expected to generate cost and time savings to families and to UK government bodies that provide financial assistance to affected families.

Eladocagene exuparvovec is a highly innovative gene replacement therapy and the first and only disease-modifying treatment for AADC deficiency. The availability of eladocagene exuparvovec will increase UK-specific first-hand experience of the therapy and will position the UK as world-leaders in AADC deficiency and in delivering highly innovative therapies to patients with the greatest unmet need. Learnings will pave the way for future innovations, both in AADC deficiency and in other genetic conditions including those that affect children. PTC is committed to enhancing patients' lives by monitoring real-world outcomes for at least 10 years following eladocagene exuparvovec therapy worldwide (including in the UK) through the AADCAware Registry.[30]

Summary

AADC deficiency is a devastating and life-shortening condition in which most patients remain bedridden for their entire life. Eladocagene exuparvovec will be the first and only licensed disease-modifying treatment that addresses the underlying genetic cause of the disease. By improving motor milestone achievement and other symptoms related to AADC deficiency, a single dose of eladocagene exuparvovec provides transformative and life-changing benefits

and has the potential to reduce premature mortality and improve quality-of-life of patients, in turn improving the lives of both patients and their carers. A NICE recommendation offers the only hope for the very few patients in the UK with this ultra-rare and devastating condition and will pave the way for substantial improvements in the way AADC deficiency is managed.

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's proposed marketing authorisation for this indication, as the therapy was under the European Medicines Agency regulatory review at the time of submission.

The marketing authorisation of eladocagene exuparvovec is for "[redacted]".[31]

Please refer to Table 1 for a summary of the decision problem.

Table 1: NICE decision problem

	Final scope issued by NICE[32]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with aromatic L-amino acid decarboxylase (AADC) deficiency	Patients [redacted]	The population aligns with the anticipated EMA and MHRA marketing authorisation.
Intervention	Eladocagene exuparvovec (Upstaza®).	Eladocagene exuparvovec (Upstaza®).	N/A
Comparator(s)	Established clinical management without eladocagene exuparvovec	Best supportive care without eladocagene exuparvovec.	In line with the final scope, but with minor wording change.
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age-appropriate motor milestones such as head control, sitting, standing, walking) including assessments through PDMS-2, AIMS, and Bayley-III totals and subscales • Autonomic nervous system functioning • Speech and language development • Change in levels of neurotransmitter metabolites (HVA and/or 5-HIAA) in the CSF • Cognitive development • Change in putaminal signal in 6-[18F] fluorodopa-PET study post-surgery. • Body weight • Mortality • Adverse effects of treatment • Health-related quality-of-life (for patients and carers)	All outcomes listed in the final NICE scope are included in the submission.	N/A
Economic analysis	• Cost-effectiveness over a lifetime time horizon using incremental cost per quality-adjusted life year • Patient access schemes (as applicable) • The nature and extent of the resources needed to enable the new technology to be used (i.e. the budget impact of the new technology)	In line with NICE scope. A patient access scheme has been approved and is included within this submission.	N/A

Subgroups to be considered	N/A	No subgroups are considered.	Limited sample size due to ultra-rare disease means data available for intervention and comparator is insufficient to allow for subgroup analyses.
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	In line with NICE scope.	N/A
Special considerations including issues related to equity or equality	There are no equity or equality issues.	In line with NICE scope.	N/A

Abbreviations: AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AIMS – Alberta Infant Motor Scale; Bayley-III – Bayley Scales of Infant Development 3rd edition: BSC – Best supportive care; CSF – Cerebrospinal fluid; HRQoL - Health-related quality-of-life; HIAA – Hydroxyindoleacetic acid; HVA – Homovanillic acid; NICE – National institute for healthcare and excellence; PDMS-2 – Peabody Developmental Motor Scale Second Edition; PET – Positron emission tomography

B.1.2. Description of the technology being evaluated

Please see Appendix C for the draft Summary of Product Characteristics. A UK Public Assessment Report was not available at the time of submission.

B.1.2.1 Eladocagene exuparvovec overview

The technology being evaluated is eladocagene exuparvovec (Upstaza®), a single dose, gene replacement therapy that addresses the underlying cause of AADC deficiency. A summary of the technology being evaluated is provided in Table 2.

Table 2: Technology being evaluated: eladocagene exuparvovec

UK approved name and brand name	• **Approved name:** Eladocagene exuparvovec • **Brand name:** Upstaza®
Mechanism of action	AADC deficiency is an inborn error of neurotransmitter biosynthesis with an autosomal recessive inheritance in the dopa decarboxylase (*DDC*) gene.[31] The *DDC* gene encodes the AADC enzyme, which converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine.[31] Mutations in the *DDC* gene result in reduction or absence of AADC enzyme activity, causing a reduction in the levels of dopamine and the failure of most patients with AADC deficiency to achieve developmental milestones.[31] Eladocagene exuparvovec is a gene-replacement therapy based on recombinant AAV2 vector containing the human cDNA for the *DDC* gene.[31] After infusion into the putamen, the product results in the expression of the AADC enzyme and subsequent production of dopamine, and consequently, development of motor function in treated AADC deficient patients.[31]
Marketing authorisation/CE mark status	Eladocagene exuparvovec is under regulatory review with the EMA, with Committee for Medicinal Products for Human Use (CHMP) opinion due in [redacted]. Eladocagene exuparvovec is expected to received UK marketing authorisation in [redacted]. The UK Medicines and Healthcare Regulatory Agency (MHRA) awarded eladocagene exuparvovec with Promising Innovative Medicines (PIM) designation on 9 June 2020.[33]
Indications and any restriction(s) as described in the SmPC	The indication for eladocagene exuparvovec is expected to be [redacted][31]
Method of administration and dosage	Eladocagene exuparvovec is a single use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen.[31] Patients will receive a total dose of $1.8x10^{11}$ vector genomes (vg) delivered as four 0.08 mL ($0.45x10^{11}$ vg) infusions (two per putamen).[31] Treatment should be administered in a centre which is specialised in stereotactic neurosurgery, by a qualified neurosurgeon under controlled aseptic conditions.[31]
Additional tests or investigations	Additional tests and investigations associated with the administration of eladocagene exuparvovec and follow-up of patients include:

	• **Diagnosis:** Eladocagene exuparvovec is for patients that have genetically confirmed AADC deficiency. It is assumed that no additional genetic testing is needed to confirm eladocagene exuparvovec eligibility. • **Pre-administration:** Patients may undergo additional pre-administration examinations compared to usual clinical practice to ensure they are suitable for treatment. These additional tests include an MRI evaluation for planning of the stereotactic surgery. Further details of pre-operative tests required prior to the administration of eladocagene exuparvovec can be detailed in Section B.3.5.1.1.2. • **Administration:** In line with the SmPC,[31] treatment of eladocagene exuparvovec should be administered by a qualified neurosurgeon in a surgical suite under controlled aseptic conditions. • **Post-administration:** As per the SmPC,[31] immediately after administration of eladocagene exuparvovec, the patient undergoes a post-operative CT scan to ensure no complications (i.e. bleeding). The patient must reside in the vicinity of the hospital where the procedure was performed for at least 48 hours following the procedure, before returning home. • **Follow-up:** As per the SmPC,[31] post-treatment care should be managed by the referring paediatric neurologist and/or with the neurosurgeon, and include at least two follow up visits. The patient will have a first follow up 7 days after surgery to ensure that no complications have developed. A second follow up visit will take place 2 weeks later (i.e. 3 weeks after the surgery) to monitor post-surgical recovery and occurrence of adverse events.
List price and average cost of a course of treatment	• List price: £[redacted] • Average cost per patient including administration, treatment acquisition, and monitoring: £[redacted]
Patient access scheme (if applicable)	• A patient access scheme involving a simple discount of [redacted] % has been approved by PASLU. • The net price of eladocagene exuparvovec is: £[redacted]

Abbreviations: AADC deficiency - Aromatic L-amino acid decarboxylase deficiency; AAV2 - Adeno-associated virus serotype 2; AIMS – Alberta infant motor scale; Bayley-III – Bayley scales of infant development, 3rd edition: BSC – Best supportive care; CHMP - Committee for medicinal products for human use; CSF – Cerebrospinal fluid; CT – Computed tomography ;DDC - Dopa decarboxylase; ECG - Electrocardiogram ; EMA – European medicines agency; HRQoL - Health-related quality-of-life; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; L-DOPA -- L-3, 4-dihydroxyphenylalanine; MHRA - UK medicines and healthcare regulatory agency; MRI - Magnetic resonance imaging; NICE – National institute for healthcare and excellence; PASLU – Patient access scheme liaison unit; PDMS-2 - Peabody Developmental Motor Scale; PET – Positron emission tomography; PIM - Promising Innovative Medicines; SMPC - Summary of product characteristics

B.1.2.2 Mechanism of action

Eladocagene exuparvovec is a gene-replacement therapy that introduces a functioning AADC enzyme in the brain of patients with AADC deficiency, in turn restoring the production of dopamine and other essential neurotransmitters

AADC deficiency is an inborn error of neurotransmitter biosynthesis with an autosomal recessive inheritance in the dopa decarboxylase (*DDC*) gene.[31] The *DDC* gene encodes the AADC enzyme, which converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine.[31] Mutations in the *DDC* gene result in reduction or absence of AADC enzyme activity, causing

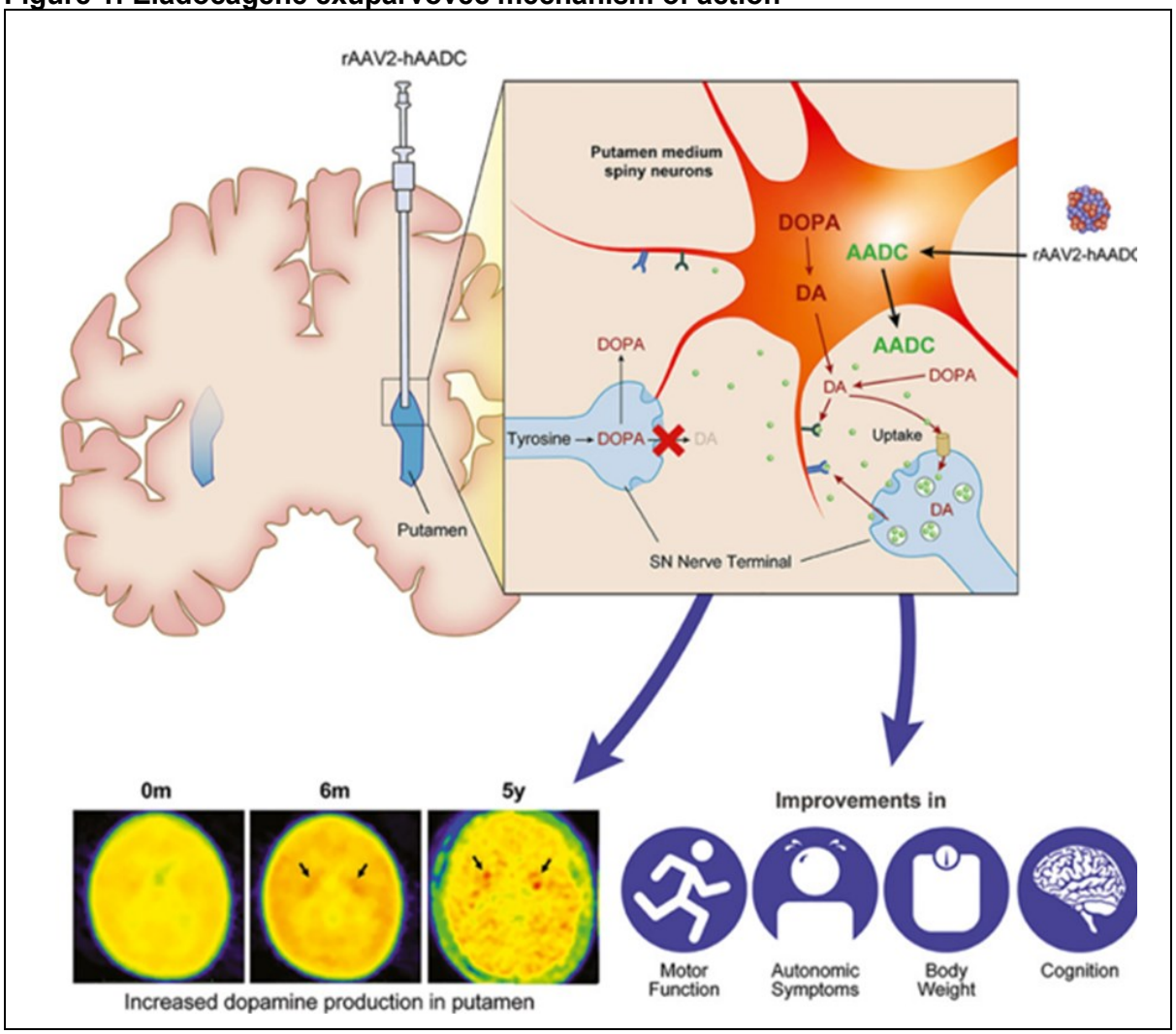
a reduction in the levels of dopamine and the failure of most patients with AADC deficiency to achieve developmental milestones.[31]

Eladocagene exuparvovec is a gene-replacement therapy based on recombinant AAV2 vector containing the human cDNA for the *DDC* gene.[31] After infusion into the putamen, the product results in the expression of the AADC enzyme and subsequent production of dopamine, and consequently, development of motor function in treated AADC deficient patients.[31] The putamen was selected as the target site for the delivery of eladocagene exuparvovec to maximise expression of the AADC enzyme and reduce the chance of AADC expression in off-target tissues of the brain, which could cause adverse effects.[34,35] Local delivery to the putamen is also expected to produce a smaller immune response compared to other routes of administration.[34,35]

The putamen is situated in the striatal/dorsal portion of the basal ganglia (found deep within the cerebral hemispheres) in the brain and directly produces the AADC enzyme, which converts endogenous L-DOPA into the essential neurotransmitter, dopamine.[36] The putamen is involved in learning and motor control, including language and cognitive functioning, and putaminal dysfunctions are linked to various motor and cognitive dysfunctions such as Parkinson's Disease, Huntington's Disease, and Alzheimer's Disease.[37] By delivering a functioning *DDC* gene directly into the putamen, eladocagene exuparvovec restores production of the AADC enzyme, in turn, restoring dopamine production.[36] Direct restoration of the DDC gene in the putamen bypasses the blood-brain barrier, and in turn the use of a micro-dose of virus, minimizing immune system response (eliminating the need for corticosteroids), off target tissue transduction, and toxicity.

Eladocagene exuparvovec provides a full copy of the *DDC* gene and is therefore agnostic to the underlying mutation causing AADC deficiency, meaning it is expected to be effective regardless of the underlying type of genetic mutation. Eladocagene exuparvovec is the first and only product licensed to treat the underlying genetic defect that causes AADC deficiency and the only licensed product that is able to modify the disease course. A summary of the mechanism of action of eladocagene exuparvovec is provided in Figure 1 and Figure 2.

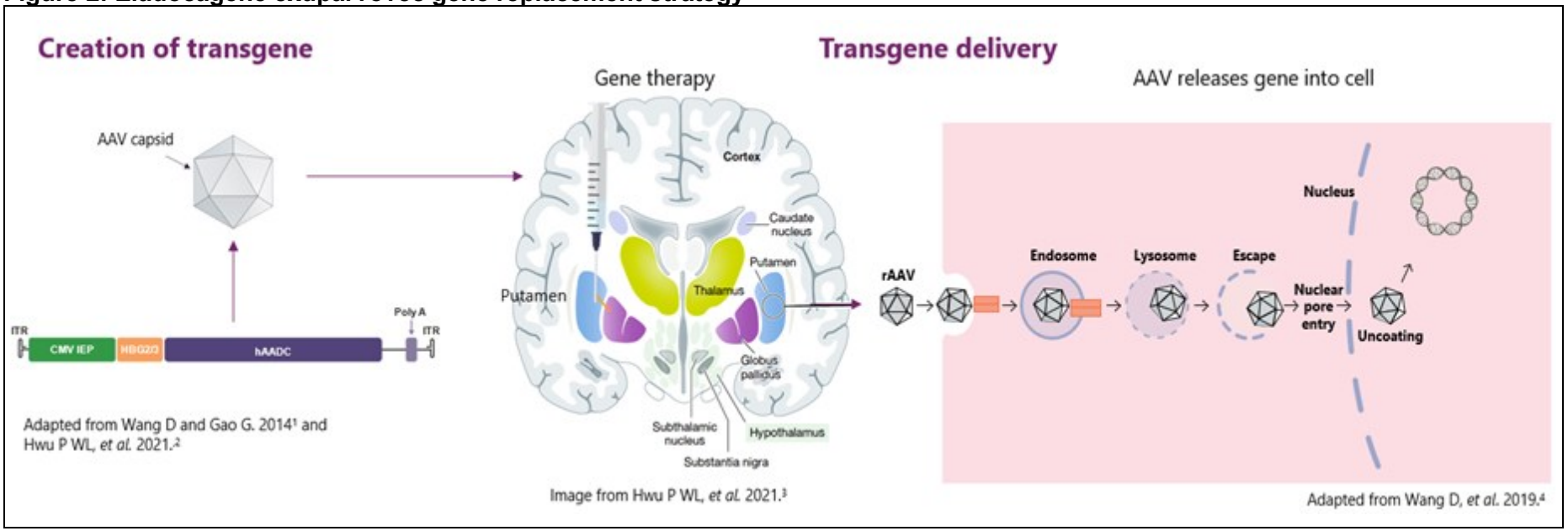
Figure 1: Eladocagene exuparvovec mechanism of action



Eladocagene exuparvovec is a gene-replacement therapy based on rAAV2-hAADC. It is injected into the putamen, restoring a functioning DDC gene. This restores the production of dopamine and other neurotransmitters, in turn leading to improved motor function, autonomic symptoms, body weight, and cognition.
Abbreviations: AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; cDNA – coding deoxyribonucleic acid; DDC – dopa decarboxylase gene; L-DOPA – levodopa; rAAV2-hAADC – recombinant adeno-associated virus vector encoding human cDNA for the DDC gene

Source: Tai *et al.* 2022 [10]

Figure 2: Eladocagene exuparvovec gene replacement strategy



Eladocagene exuparvovec is a gene replacement therapy based on rAAV2-hAADC. It is infused into the putamen, restoring a functioning DDC gene. This restores the production of dopamine and other neurotransmitters, in turn leading to improved motor function, autonomic symptoms, body weight, and cognition.
Abbreviations: AAV - Adeno-associated virus; cDNA, - Complementary DNA; CMV IEP - Human cytomegalovirus immediate-early promoter; hAADC, - Human aromatic L-amino acid decarboxylase; HBG2/3 - Human beta globin partial intron 2/partial exon 3; ITR - AAV2 inverted terminal repeat; poly A - Polyadenylation-containing sequence; rAAV2 - Recombinant adeno-associated virus vector.
Source: PTC Therapeutics 2022[38]; Wang D and Gao G. Discov Med. 2014;18(97):67–77;[39] Hwu P WL, et al. 2021[40]; Hwu P WL, et al. 2021[36]; Wang D, et al. Nat Rev Drug Discov. 2019;18(5):358–378.[41]

B.1.2.3 Mode of administration

Eladocagene exuparvovec is one-dose gene-replacement therapy that provides lifetime benefits following a single neurosurgical session

Eladocagene exuparvovec is a single use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen.[31] Patients will receive a total dose of $1.8x10^{11}$ vector genomes (vg) delivered as four 0.08 mL ($0.45x10^{11}$ vg) infusions (two per putamen).[31] Treatment should be administered in a centre which is specialised in stereotactic neurosurgery, by a qualified neurosurgeon under controlled aseptic conditions.[31]

Four separate infusions of equal volumes are performed to the right anterior putamen, right posterior putamen, left anterior putamen, and left posterior putamen.[31] The target infusion sites are defined per standard stereotactic neurosurgical practice.[31] Upstaza® is administered as a bilateral infusion (2 infusions per putamen) with an intracranial cannula.[31]

Eladocagene exuparvovec is a one-dose treatment that is infused into the bilateral putamen via well-established stereotactic surgery (a minimally invasive surgical technique that is widely used in neurosurgery).[14] Following the single neurosurgical session, patients receive life-long benefits with no need for further administrations of eladocagene exuparvovec.

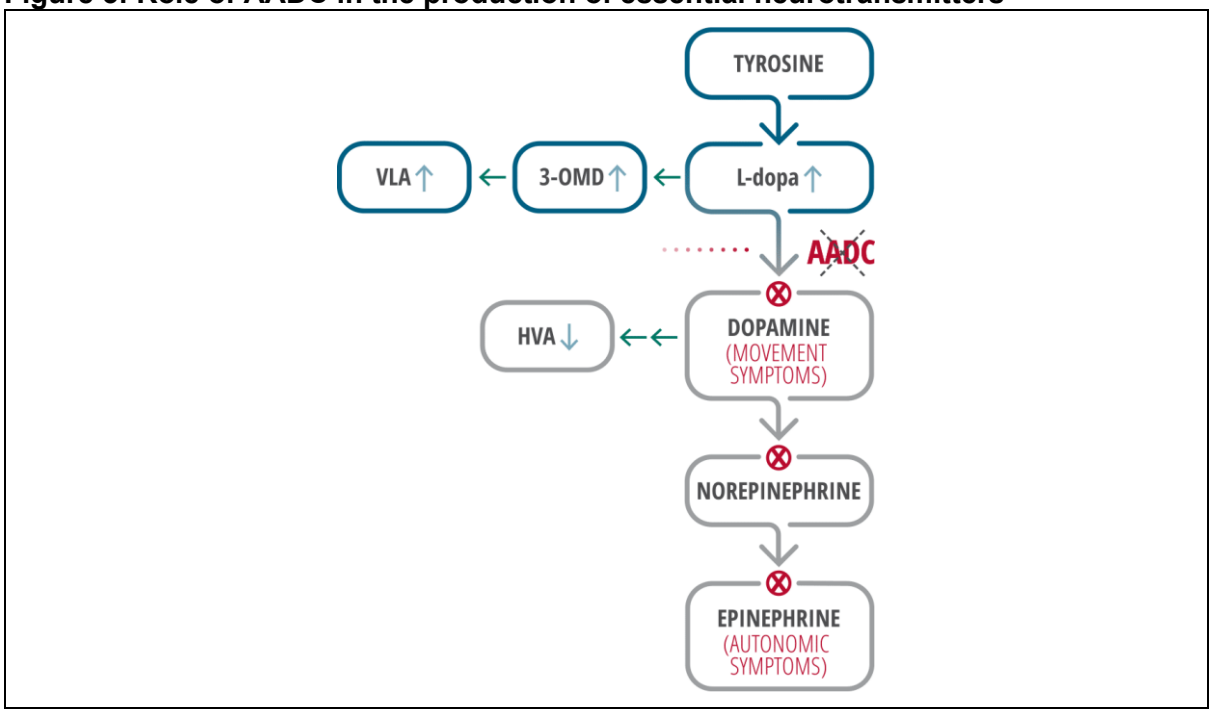
B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

AADC deficiency is an ultra-rare genetic disorder severely affecting motor development

AADC deficiency is an ultra-rare, genetic, fatal disorder often resulting in death before the first decade of life.[1] It is characterised by a mutation in the *DDC* gene, which causes an absence of the AADC enzyme and in turn leads to severe deficiency of dopamine and other essential neurotransmitters (Figure 3).[2] The AADC enzyme is integral to many highly interlinked catalytic and metabolic pathways that control the levels of aromatic amines and, in turn, the synthesis of dopamine and other neurotransmitters.[2,3,6] While some patients can have AADC deficiency without a severe phenotype, ~80% of patients are classified as having a severe phenotype[2] and are the focus of this submission.

Figure 3: Role of AADC in the production of essential neurotransmitters



Note: epinepherine is chemicaly identical to adrenaline, norepinepherine is chemically identical to noradrenaline.
Abbreviations: 3-OMD – 3-O-methyldopa; 5-HIAA – 5-hydroxyindoleacetic acid; 5-HTP – 5-hydroxytryptophan; HVA – homovanillic acid; L-dopa – L-3,4-dihydroxyphenylalanine; VLA – vanillactic acid.
Source: AADC Insights 2022[42]

Severe AADC deficiency significantly impacts patients from birth onwards, affecting major aspects of their development, motor skills, growth, cognitive and language skills, and behaviour.[2,3,6] The most common characteristic of severe AADC deficiency is lack of motor development, with the majority of patients remaining bedridden for their lifetime. In one natural history study, 97% of patients failed to achieve any motor milestones typically associated with child development[6] (e.g. head control, sitting unassisted, standing with support, and walking with assistance; see Figure 4).

Figure 4: Motor development in a normal child versus a child with AADC deficiency

Abbreviations: AADC – aromatic L-amino decarboxylase deficiency
Source: About AADC 2022[9]

In addition to affecting motor development, severe AADC deficiency causes regular and prolonged seizure-like episodes and a wide range of movement, cognitive, emotional, and autonomic disorders

In addition to failing to develop, patients suffer a range of neurologic and cognitive impairments, including hypotonia (low muscle tone/floppiness), movement disorders including dystonia (involuntary muscle contractions), hypokinesia (smaller than expected movements), and regular seizure-like episodes of oculogyric crises [OGC] during which the child's eyes roll upward without control and they experience tongue thrusting, jaw spasms, hyperextension of the head/neck/back, and involuntary contractions (see Figure 5).[9] Patients also experience excessive crying, sleeping problems, irritability, problems with digestion, cognitive impairment, developmental delay, and autonomic symptoms.[2,9] The severe and devastating nature of AADC deficiency is highlighted in videos in Tai *et al.* (2022).[10]

Figure 5: Characteristics of AADC deficiency

Patient with AADC deficiency in Taiwan presenting with (a) involuntary tongue thrusting, (b) oculogyric crisis, and (c) muscle spasm
Source: Dai et al., 2020[43]

Dopamine deficiency underpins the wide range of symptoms in severe AADC deficiency

Dopamine deficiency is a key driver of the pathology of AADC deficiency given its role in cognitive function, voluntary movement, and emotion.[3,44] Dopamine is also the precursor for adrenaline and noradrenaline, and a reduction in adrenaline and noradrenaline affects mood, attention, sleeping habits, cognition and stress hormone levels.[3,6] A combined deficiency in these neurotransmitters leaves children with profound and devastating neurological and developmental failure.

Severe AADC deficiency is ultra-rare, with [redacted] expected in the UK each year

AADC deficiency is extremely rare, with an estimated 853 patients living with the disease in the EU (including the UK), indicating a prevalence of 1:118,000.[2,3,6] As of 2021, only 237 patients across the world have been described in the literature and confirmed as unique cases of AADC deficiency (based on data from a comprehensive natural history database developed by PTC).[45] There are currently 9 known patient(s) in the UK with AADC deficiency, equating to a current UK prevalence of approximately 1 in 7.5 million. It is expected that [redacted] would be diagnosed [redacted] in the next [redacted].[5] This highlights the rarity of AADC deficiency.

B.1.3.2 Diagnosis and presentation

AADC deficiency is challenging to diagnose due to its rarity

Given its rarity and varying symptoms, AADC deficiency can be challenging to diagnose.[46] Symptoms of AADC deficiency may be mistaken for other diseases, such as motor/movement disorders (e.g. Parkinson's disease and cerebral palsy) and seizure disorders (e.g. epilepsy).[2] In a retrospective study by Pearson *et al.* (2020), 27% (14/52) of patients were initially diagnosed with epilepsy or given anti-epileptic treatments before a diagnosis of AADC deficiency was reached.[7] Patients may require multiple visits to a wide range of specialists before a confirmed diagnosis is reached. Diagnosis is usually achieved following confirmation from two of three tests: (1) analysing the pattern of cerebrospinal fluid (CSF), (2) monitoring AADC enzyme activity in plasma, and (3) genetic testing of the DDC gene.[2] In the UK, 2 out of the 3 tests are required for a confirmed diagnosis, with genetic testing usually performed.

The majority of AADC deficiency patients have a severe phenotype, defined as no or poor head control at 24 months of age

While there is no standard clinical practice regarding diagnosing AADC deficiency, a 2017 consensus guideline by Wassenberg *et al*. 2017 provided a framework and broadly classified AADC deficiency into mild, moderate, and severe phenotypes. A mild phenotype is defined as a mild delay in developmental milestones, no requirement for ambulatory assistance, and mild intellectual disability, while a severe phenotype is defined as achieving no or very limited developmental milestones and being fully dependent.[2]

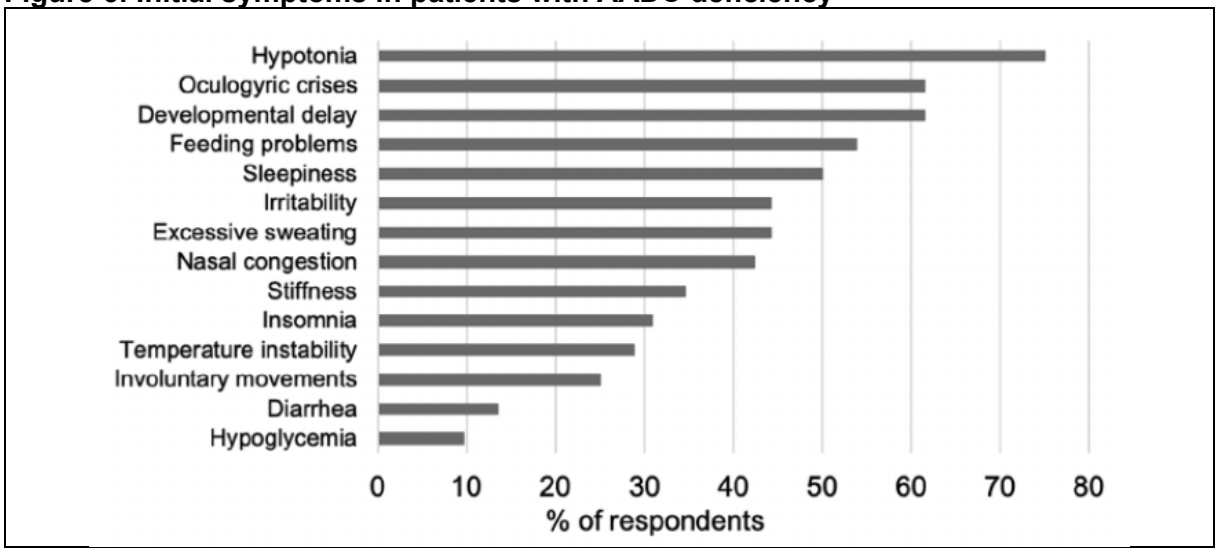
Most patients have a severe phenotype of AADC deficiency. Among 103 patients described by Wassenberg, 82 (80%) were classed as severe and 6 (6%) were mild, aligning with a natural history study (Hwu *et al*., 2019) describing 36 of 37 (97%) patients as severe.[2,6] Similarly, in a natural history database developed by PTC comprising 237 patients that have been described in the literature to date, of the 96 patients whose phenotype could be classified, 69 (72%) were identified as having a severe phenotype (no or poor head control at 24 months of age), while 27 (28%) were mild or moderate.[8]

AADC deficiency symptoms are wide-ranging, severe, and present from birth

AADC deficiency typically presents from birth. According to Wassenberg *et al*. (2017) the mean age of symptom onset is just 2.7 months[2] and nearly all patients have their first

symptoms before 6 months.[7] Typical initial symptoms include hypotonia, oculogyric crisis (OGC), developmental delay, poor head control, excessive crying, ptosis (drooping eyelids), feeding/swallowing problems, temperature instability, and other gastrointestinal problems (Figure 6).[2] The wide-ranging symptoms have a devastating impact on patients and their family caregivers.

Figure 6: Initial symptoms in patients with AADC deficiency



Data from 52 patients with AADC deficiency of all severity types, as reported by caregivers/clinicians in a global survey
Abbreviations: AADC deficiency - aromatic L-amino acid decarboxylase deficiency
Source: Pearson et al., 2020[7]

Despite early onset of symptoms, a diagnosis of AADC deficiency may be delayed and often requires multiple healthcare visits

Despite the early onset of symptoms, the mean age of diagnosis is reported to be 3.2[8]–3.5[2] years, and some people are undiagnosed until the age of 23 years.[2] This indicates the challenges of diagnosing AADC deficiency, with caregivers reporting having seen a mean of 8 (1-24) healthcare professionals before a diagnosis was achieved.[13] New diagnostic tools, such as neonatal screening using dried blood spot testing, may help to achieve an earlier diagnosis and therefore help to improve patient outcomes.[47]

B.1.3.3 Symptoms of AADC deficiency

B.1.3.3.1. Symptom overview

AADC deficiency has severe, wide-ranging and lifelong symptoms

AADC deficiency is associated with a wide range of severe symptoms predominantly impacting the central nervous system (CNS), autonomic nervous system, gastrointestinal system, and endocrine system. In a review of 117 patients described in the literature, Wassenberg *et al.* 2017 noted 44 symptoms and signs impacting tone regulation, movement, development, behaviour, sleeping, homeostasis, feeding, and heart functioning (Figure 7). While some symptoms emerge later than others, once a symptom emerges it typically persists

throughout a severe patient's lifespan, with little sign of improvement over time or with treatment.[2] This shows the devastating and broad-ranging challenges faced by patients with AADC deficiency and their families (see Sections B.1.3.6 and B.1.3.7 for the patient and caregiver impact of AADC deficiency).

Figure 7: Symptoms associated with AADC deficiency over a patient's lifetime

		Symptom/ sign	Neo natal	Infancy	Child hood	Adolescence	Adulthood
CNS	Tone regulation	Floppy infant	+	++			
		Hypotonia (mainly truncal)	+	++	++	++	++
		Poor head control	+	+	+	+	+
		Hypertonia (mainly limbs)	+	+	+	+	+
	Movement disorders	Dyskinesia (eg hyperkinesia, chorea, athetosis)	±	+	+	+	+
		Dystonia	-	++	++	++	++
		Oculogyric crisis	±	++	++	++	++
		Hypokinesia and/ or bradykinesia	±	++	++	++	++
		Myodonus	±	±	±	±	±
		Tremor	±	±	±	±	±
	Developmental Delay	Delayed motor development	±	++	++	++	++
		Delayed cognitive development		±	+	+	+
		Delayed speech development		±	+	+	+
	Behavioural Problems	Irritability	++	++	+	+	+
		Autistic features			±	±	±
		Dysphoria/ Mood problems	±	±	±	±	±
		Excessive crying	+	++	+	-	-
	Sleeping Problems	Insomnia and or hypersomnia		+	+	+	+
	Other	Epileptic seizures	-	±	±	±	±
		Fatiguability	±	±	±	±	±
		Diurnal fluctuation		±	±	±	±
		Dysarthria			±	±	±
		Poor eye fixation		+	+	+	+
		Increased startle	±	±	±	±	±
ANS	Eyes	Ptosis	+	+	+	+	+
		Miosis	±	±	±	±	±
	Upper respiratory tract	Nasal congestion	-	+	+	±	±
		Excessive drooling	-	+	+	±	±
		Stridor	±	±	±	±	±
	Skin	Excessive sweating	-	+	+	+	+
	Homeostasis	Temperature instability	+	+	+	+	+
	Cardiovascular	(Orthostatic) Hypotension	-	-	±	+	+
		Bradycardia	±	±	±	±	±
		Heart rhytm abnormalities	±	±	±	±	
	Gastrointestinal	Diarrhea	±	+	+	+	±
		Obstipation	±	+	+	+	±
Metabolic/ endocrine		Hypoglycemia	±	±	±	-	-
		Hyperprolactinemia	±	±	±	±	±
General		Feeding/ Swallowing Problems	+	+	+	+	+
		Gastrointestinal reflux	+	+	+	±	±
		Gastrointestinal problems unspecified	+	++	+	+	+
		Failure to thrive	±	+	+	+	
		Contractures	-	-	-	±	±
		Small hand and feet	±	±	±	±	±

Notes: Symptoms described in AADC deficiency among 117 cases of all severities reported in the literature.++ very often, + often, ± sometimes, - not expected. Abbreviations: AADC deficiency - aromatic L-amino acid decarboxylase deficiency ; ANS – autonomic nervous system; CNS - central nervous system
Source: Wassenberg et al. Orphanet Journal of Rare Diseases (2017)[2]

B.1.3.3.2. Motor and developmental deficits

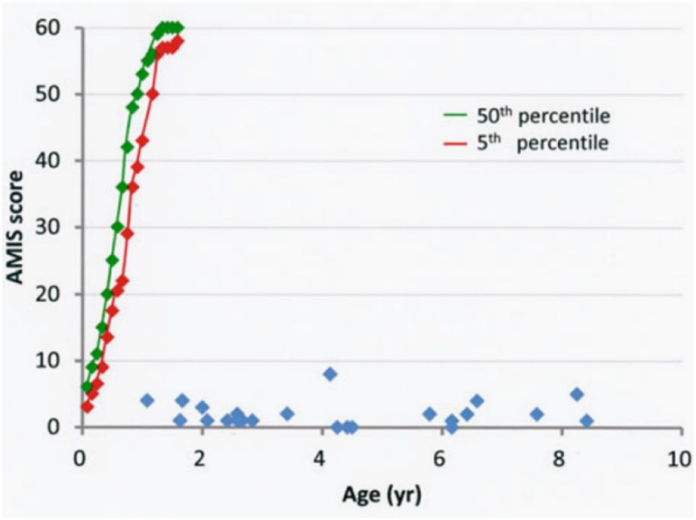
Nearly all patients with severe AADC deficiency are bedridden and completely dependent throughout their lifetime, achieving no motor milestones

AADC deficiency causes severe motor and developmental deficits. Most patients with severe AADC deficiency will never be able to hold their head up, sit by themselves, stand, or speak[6], and are bedridden all their lives, with complete dependence on their carer (usually a family member).[6] Due to the lack of disease-modifying treatments, many patients will never achieve any motor milestones at any point throughout their lives.[6] The impact of AADC deficiency on motor function is emphasised in videos reported in Tai *et al.,* (2022)[10] and as part of the EMA Scientific Advisory Group video of Patient 311.[19]

To gain insight into the natural history of AADC deficiency, PTC conducted a systematic literature review of reported case studies of AADC deficiency patients and used the evidence to develop a patient-level Natural History Database (NHDB).[8] Among 96 unique patients with data on severity, 69 (72%) were classified as having no or poor head control at 24 months of age.[8] The high current unmet need of this devastating disease is shown by the fact that only 2 of the 69 severe patients (3%) had any improvement in motor function with current best supportive care (BSC) treatments.[8] The remaining 97% of patients are likely to have remained bedridden and completely dependent for the entirety of their shortened lives.

Similar findings were reported in a natural history study by Hwu *et al.* 2017 consisting of 37 patients (36 classified as severe) with a mean age of 1.1 years (range: 0.0–7.3 years).[6] Of the 22 patients (mean age 0.9 years) with motor function data (as measured by PDMS-2 and AIMS; instruments described in Table 3), motor function was far below that of a normal infant.[6] Median total raw PDMS-2 score was just 9 (range: 2–26), which is below the first percentile of children without AADC deficiency of the same age (i.e. 99% of children in the general population have a higher score)[6]. The median total raw AIMS score was 1 (range: 0-8), which was far below the fifth percentile of normal infants aged 0–18 months. The AIMS data indicate that 95% of normal infants aged 0–18 months have a higher score than children with AADC deficiency achieve at up to 8 years of age (Figure 8).[6] In addition, there was no correlation between age and raw AIMS or PDMS-2 score, showing that patients fail to develop any motor function as they age.[6] This clearly illustrates the severe motor and developmental issues affecting patients with AADC deficiency.

Figure 8: AIMS score in 22 patients with severe AADC deficiency



Data from patients (blue diamond) are depicted according to the age at the time of measurement. The red diamonds indicate the fifth percentile and the green diamonds indicate the 50th percentile of normal children. The data highlight that patients with AADC deficiency achieve virtually no gross motor development.
Abbreviations: AADC deficiency – aromatic L-amino decarboxylase deficiency; AIMS – Alberta Infant Motor Scale
Source: Hwu et al., 2017[6]

Table 3: Instruments for assessing infant development

Instrument	Description

Peabody Development Motor Scales (Second Edition)[48]	• PDMS-2 is a well-established instrument administered to children from birth and is composed of four gross motor and two fine motor subtests. It is a widely used measure of motor function and is validated in AADC deficiency.
	• Each subtest is further divided into a number of items, with each item scored out of 2 (0 = no development, 1 = partial mastery, 2 = mastery).
	• Gross motor subtests:
	  ○ Reflexes: 8 items assessing reactions to environmental events, measured from birth to 11 months
	  ○ Stationary: 30 items assessing body control, centre of gravity, and equilibrium
	  ○ Locomotion: 89 items assessing movement including crawling, walking, running, hopping, and jumping forward
	  ○ Object manipulation: 24 items measured from 12 months onwards, assessing manipulation of a ball including catching, throwing, and kicking
	• Fine motor subtests:
	  ○ Grasping: 26 items assessing hand function including holding an object and individual finger control
	  ○ Visual-motor integration: 72 items assessing hand-eye coordination, such as reaching and grasping and using building blocks and copying design
	• PDMS-2 is widely validated across many different countries and diseases and is the only motor function instrument that can be administered from birth.[49]

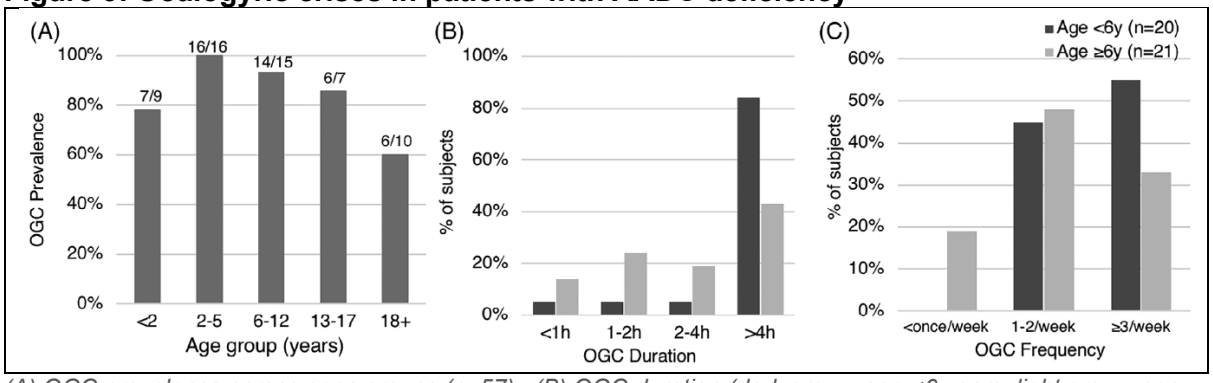
Alberta Infant Motor Scale[6]	• AIMS is a well-established instrument for measuring gross motor skills from birth through to independent walking. • It assesses the sequential achievement of motor milestones. • Assessments are conducted in four positions: prone, supine, sitting, standing.
Bayley-III	• The Bayley-III scale assesses infant and toddler development across five domains: language (receptive and expressive), motor (gross and fine), social-emotional, and adaptive.[50]

B.1.3.3.3. Oculogyric crises

All AADC deficiency patients experience weekly and potentially fatal seizure-like OGC episodes, each usually lasting for over 4 hours

The suffering caused by the lack of motor development in patients with AADC deficiency is exacerbated by other motor and functional symptoms, such as episodes of distressing seizure-like oculogyric crisis (OGC). OGCs are episodes characterised by involuntary eye movement (usually upwards), dystonia (i.e. involuntary spasms, tremors), irritability, and involuntary biting of the tongue and lips.[7,35] According to a 2020 study by Pearson *et al*., OGCs occurs in all patients, regardless of AADC deficiency severity, with most patients experiencing each episode for hours at a time and experiencing over three episodes a week (Figure 9).[7,46] OGCs can even cause death, with 2 of the 5 patients who died in the Pearson study dying from acute complications during an OGC episode.[7] UK clinical experts stated that OGCs are a key and distressing feature of AADC deficiency, with frequency correlated to AADC deficiency severity.[5]

Figure 9: Oculogyric crises in patients with AADC deficiency



(A) OGC prevalence across ages groups (n=57). (B) OGC duration (dark grey = age <6 years, light grey = age ≥6 years).(C) OGC frequency (dark grey = age <6 years, light grey = age ≥6 years)
Abbreviations: AADC - Aromatic L-amino acid decarboxylase; h - Hours; OGC - Oculogyric crisis; y - Years
Source: Pearson 2020[7]

B.1.3.4 Movement and autonomic symptoms

AADC deficiency severely impacts movement, feeding and digestion and is associated with sweating, infections, and distressing episodes of excessive crying

In addition to OGCs, patients with AADC deficiency experience other motor and non-motor disorders, including floppiness, dystonia, hypotonia, dyskinesia and hyperkinesia.[2] Non-motor symptoms in patients with AADC deficiency include nasal congestion, excessive sweating, hypoglycaemia, upper respiratory tract infection and relentless crying due to increased irritability.[2,35] Feeding problems are also a common symptom of AADC deficiency, with many patients forced to eat through a tube due to the inability to swallow, the risk of choking, and a

general disinterest in food.[35,51] Some patients have a feeding tube due to gastrointestinal symptoms.[51] Feeding problems, along with affected growth, means patients with AADC deficiency can be below average weight for a child of their age, or have impaired nutrition.[6,51]

Taken together, most patients with severe AADC deficiency suffer from severe and wide-ranging symptoms, leaving them dependent on round-the-clock care for their entire lives. Treatments that can address the underlying genetic cause, if used early enough in the developmental process, could help to alleviate symptoms and restore patients to a level of development and motor control similar to a healthy age-matched person.

B.1.3.5 Life expectancy

The limited published data on AADC deficiency survival suggest that most patients with severe AADC deficiency die before they are 10 years of age due to comorbidities associated with the condition

AADC deficiency is extremely rare[3] and poorly understood. Survival data for AADC deficiency is very limited and variable, and there are no published UK survival data. UK clinical experts are unable to provide accurate estimates of life expectancy due to the extremely rare nature of the disease, and the fact that each clinician has personally only seen a handful of patients in their lifetime.[5]

Most studies that report survival data show that patients with severe AADC deficiency suffer premature mortality.[1,2,35] In a natural history of disease study by Hwu *et al*. 2012, a mean life expectancy of 4.6 years was calculated (based on 10 respondents who completed a questionnaire sent out to the AADC deficiency patient association), suggesting that most patients die within the first decade of life.[35] Das *et al*. 2019 also reports that the life expectancy of AADC deficiency patients is under a decade.[11] In a retrospective study by Pearson *et al.* 2020 with 63 patients, the mean age of death was 9 years among the five patients who died.[7]

The cause of death in AADC deficiency is variable. Many causes of death have been reported, mainly due to comorbidities of the disease, including motor dysfunction[52], multiple organ failure[35], pneumonia,[7,44] acute complications during an OGC episode,[7] and asphyxia.[44] More research is needed to understand the lifespan of patients with AADC deficiency and the typical causes of death.

International clinical experts agree that AADC deficiency survival is correlated with motor development

In the absence of robust published estimates of life expectancy, PTC conducted an advisory board and survey involving 23 clinicians with experience treating AADC deficiency or similar conditions across Asia (n=1) Europe (n=9; including 2 UK), the Middle East (n=1), South America (n=9), and the United States (n=2). Among the 9 experts who had direct experience treating AADC deficiency and who responded to the question, two-thirds estimated life expectancy to be over 10 yearsand one-third estimated less than 10 years. Respondents were

almost unanimous that survival would correlate with the level of motor milestone achieved, as reported by 93% (14/15) of experts with AADC deficiency experience and 100% (6/6) of experts without direct experience.[53] Consultation with UK clinical experts indicated that severe AADC deficiency patients are unlikely to live into their teenage years.[5] UK clinical experts also agreed that improved motor milestones would likely lead to improved survival in patients with AADC deficiency.[5]

Evidence from proxy diseases highlights a correlation between motor function and patient survival

Given the very limited life expectancy data in AADC deficiency, disease proxies may be used. In a clinical advisory board, 73% of experts with direct AADC deficiency experience agreed that cerebral palsy (CP) is a suitable proxy for survival, while only 7% felt spinal muscular atrophy was a suitable proxy for survival.[54] In line with this, 74% of clinicians agreed on the mapping of CP motor milestone-related survival estimates to motor milestone states in AADC deficiency.[54] UK clinical experts agreed that CP is the closest proxy to AADC deficiency in terms of mortality and that it is not possible to estimate survival in AADC deficiency based on data from patients with AADC deficiency alone.[5]

CP is a good proxy for AADC deficiency as both conditions involve motor impairment and epilepsy.[55] According to a study on the long-term survival and mortality of patients with CP in Australia (Blair *et al.*, 2019), standardised mortality ratios (SMR) increase with increasing overall disability score (DISAB; an instrument measuring motor function with a score of 1 [minimal hemiplegia with no additional impairment] to 12 [severe quadriplegia, bilateral blindness, deafness, active epilepsy, severe cognitive impairment]). Patients with CP with a DISAB score of ≤3 (low impairment) have a similar risk of death as age-matched members of the general population, whereas those with SMRs ≥11 have a 100-times greater risk of death.[55]

The life expectancy of a patient with CP strongly depends on the level of disability at a given age. If a patient has severe impairments in childhood (DISAB score ≥9 at age 1-5 years), they are expected to live until the age of 35-40 years, whereas if they have less severe CP in childhood (DISAB score of 6-8 at age 1-5 years), they are expected to live to 60-65 years of age.[55] These data may help to estimate life expectancy in patients with AADC deficiency based on their motor milestone achievement.

B.1.3.6 Patient quality-of-life

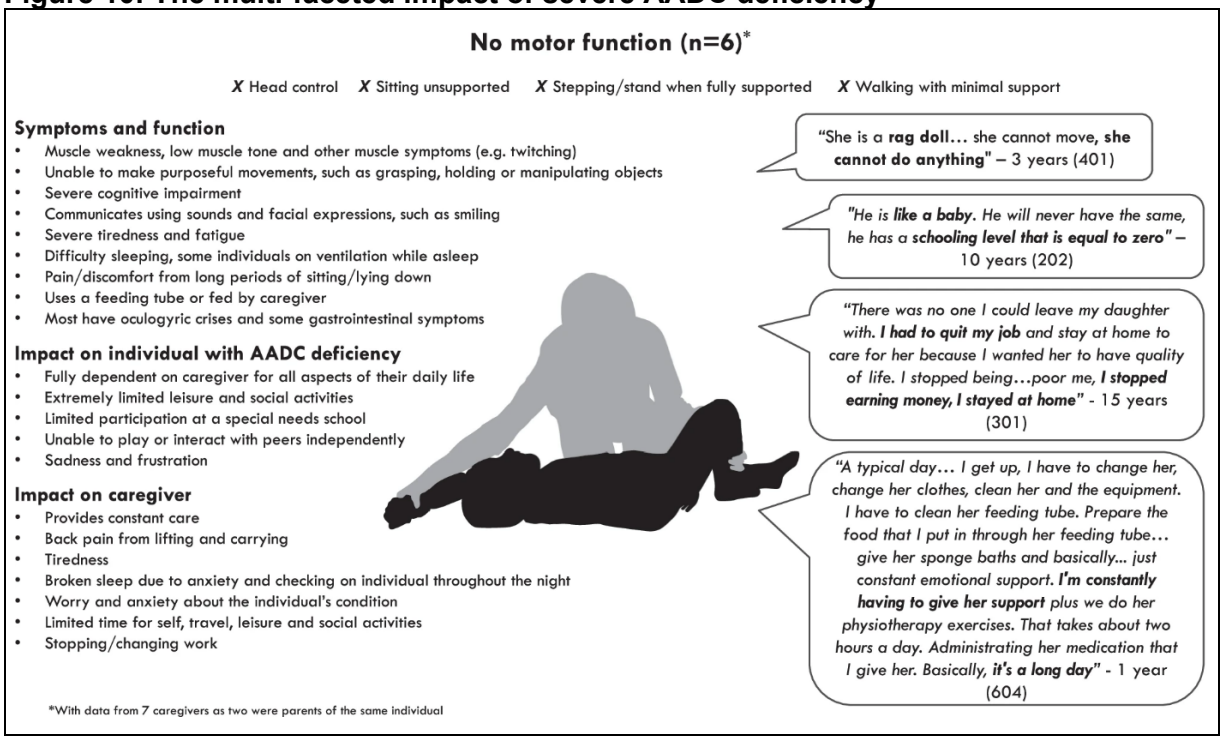
B.1.3.6.1. Overview

AADC deficiency is multi-faceted and has a profound impact on patient quality-of-life.

As an ultra-rare disease with heterogeneous and severe symptoms impacting infant development, communication, and cognition, there is very limited literature on the quality-of-life of patients with severe AADC deficiency. Most reports qualitatively describe the quality-of-life and patient and caregiver impact of the disease.

As described in Section B.1.3.3, AADC deficiency has a wide range of symptoms impacting multiple bodily systems including motor function, cognition, and the gastrointestinal system (Figure 10). This means the quality-of-life impact of AADC deficiency on patients and caregivers is profound.

Figure 10: The multi-faceted impact of severe AADC deficiency



Abbreviations: AADC deficiency - Aromatic L-amino acid decarboxylase deficiency
Source: Williams et al. 2022[11]

B.1.3.6.2. Physical wellbeing

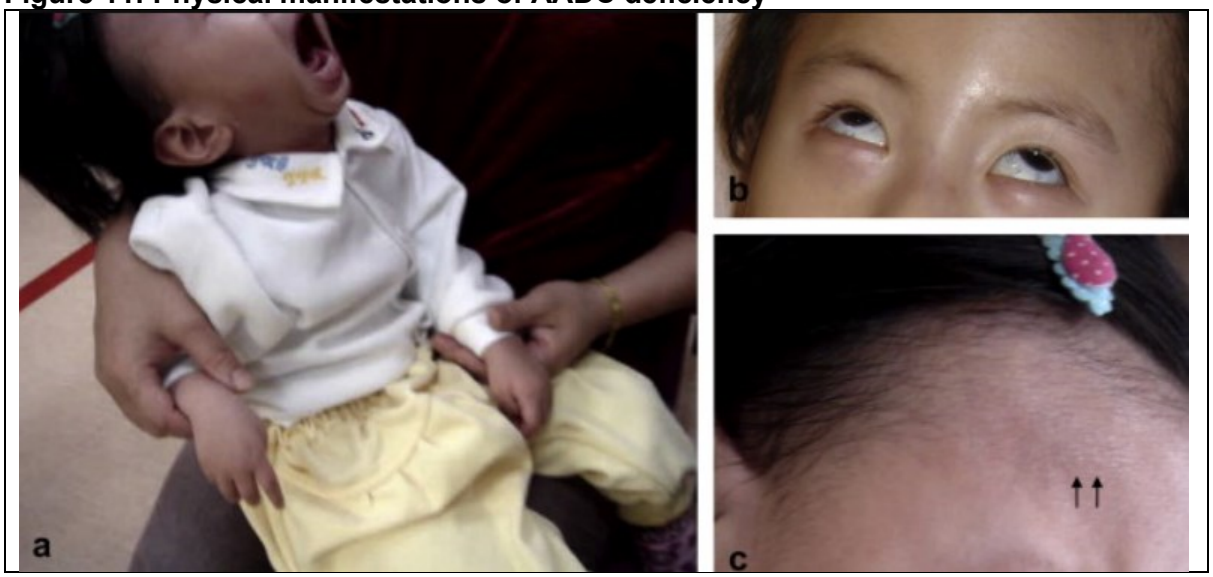
Patients with severe AADC deficiency achieve no motor function and wide-ranging movement disorders throughout their shortened lifetime

The physical impact of AADC deficiency is devastating and is evident from the first months of life. Patients with a severe phenotype of AADC deficiency fail to achieve motor milestones throughout their lifetime, with most patients unable to move, hold their head up, sit unsupported, stand, walk, and use their upper limbs.[2] It is common for many patients to be bedridden for their lifetime due to the failure to achieve motor milestones.[56] In a natural history study by Hwu *et al.* 2017 involving a cohort of 37 patients, 36/37 of the patients had profound motor deficits characterised by the inability to hold their head, sit, stand or speak.[6] Similarly, in the NHDB compiled by PTC, 69/96 patients (72%) had no motor function (i.e. poor or no head control) and only 3% of patients achieved any motor milestones in their lifetime.[8]

The absence of motor development is accompanied with episodes of distressing seizure-like OGC (involuntary eye deviations accompanied by involuntary movements of the neck, face, tongue or limbs that lasts for from seconds up to hours).[7,35,57] Patients also experience dyskinesia (erratic movement of the limbs, face or trunk), dystonia (involuntary and painful muscle contractions), hypo- and hyper-kinesia (diminished and excessive muscle movement) and hypotonia (decreased muscle tone).[2,6,7] In a study conducted by Pearson *et al.* 2020 with a cohort of 63 patients (of which 44 were severe and 8 were moderate), the most commonly reported initial non-motor symptoms were hypotonia (75%), OGCs (62%) and developmental delay (62%).[7] The occurrence of OGCs in the past and present was reported for 98% of patients,[7] highlighting the prevalence of this particularly distressing symptom.

Figure 11 visually represents the immense physical stress that patients with AADC deficiency face daily.[57] Since the age of just two months, this AADC deficiency patient presented profound floppiness, OGC episodes, nasal congestion, and excessive crying resulting in breath holding and sweating. For further visual evidence of the devastating nature of AADC deficiency, please refer to patient videos in Tai *et al.* (2022)[10] and the EMA Scientific Advisory Group video of patient 311.[19]

Figure 11: Physical manifestations of AADC deficiency



Abbreviations: AADC deficiency - Aromatic L-amino acid decarboxylase deficiency
Note: Symptoms presented from two months of age. At age two years, the patient was a) still floppy and unable to sit and showed relatively small hands from stunted growth, b) experience OCG episodes lasting up to 6 hours,

and c) regularly had beads of sweat from physical exertion.
Source: Lee et al., 2009[25]

The physical symptoms of AADC deficiency have a profound impact on patient QoL

The severe, debilitating, and wide-ranging symptoms of AADC deficiency have an impact on patient physical QoL. In a qualitative study on symptoms and impacts of AADC deficiency, caregivers emphasised the severity of the motor impairments:[58]

> *"He has no muscle tone and this doesn't help him, he cannot control his head, his arms, his legs, he cannot control his motion"[58]*

They also highlighted the distressing nature of OGC episodes, which occur regularly in almost all patients throughout their lifetime:

> *"The first thing I notice is her stare. Her eyes seem empty, she seems to be in another world. Her eyes roll upwards a lot…And she chews her tongue a lot. She starts moving, the arms also start to tremble, and she shivers. It is hard to control, it is difficult."[11]*

Furthermore, patients with AADC deficiency are often underweight due to feeding and swallowing problems, digestive problems, and a general lack of interest in food. A feeding tube is often necessary to ensure the patients receive adequate nutrition.[6,51] In a study by Pearson *et al.* 2020 with a cohort of 63 patients (44 of which are classed as having a severe phenotype), 54% reported feeding problems as an initial symptom.[7]

Sleep disturbance, difficulty falling asleep and difficulty remaining asleep is also common in many patients with AADC deficiency.[59] In Pearson *et al.* 2020, insomnia was present in 86% of patients ages 2-12 years old.[7] The reasons for sleeping problems aren't always clear, but carers of patients claim it is due to pain, discomfort, or seizures throughout the night.[51] Notably, caregivers report that their child with severe AADC deficiency is always tired and fatigued yet frequently has trouble sleeping, with some requiring melatonin and mechanical ventilation to help with sleep problems.[11] Given that people with chronic insomnia have significantly lower quality-of-life than good sleepers,[60] sleep disturbance in patients with AADC deficiency is expected to have a profound impact on physical and emotional well-being.

In addition to the above issues, patient quality-of-life is expected to be impacted by life-threatening complications associated with AADC deficiency, such as respiratory infections and gastrointestinal problems,[2,7] and by side-effects associated with extensive treatment plans.[46]

Taken together, the multi-faceted and severe physical burden of AADC deficiency is expected to have a major impact on the physical quality-of-life of patients.

B.1.3.6.3. Emotional wellbeing

Severe AADC deficiency is a highly distressing disease as evidenced by excessive crying and irritability in affected children

AADC deficiency is an unrelenting disease with severe motor, function, and cognitive deficiencies[2], and is expected to cause exceptional pain, discomfort, and frustration. Overall, it is difficult to evaluate the emotional wellbeing of a patient with AADC deficiency due to their inability to communicate and the fact they know no other life outside of their one of extreme suffering.

From the available literature, patients with AADC deficiency often feel extreme frustration at the inability to do things for themselves and to communicate their needs to carers or others, and this feeling of frustration leads to excessive crying and irritability.[51] In a cross-sectional study conducted by Pearson *et al.* 2020 involving 63 patients with AADC deficiency (44 severe, 8 moderate, 11 mild), irritability was reported in 85% of children aged 6-12 years and in 40% of subjects overall.[7] As well as excessive crying and irritability, patients experience dysphoria (general unease and unhappiness).[2]

In a qualitative study regarding the symptoms and impacts of AADC deficiency on patients, caregivers reported that their child was "quite sad" and would often cry.[51] Caregivers also highlighted the emotional and behavioural burden for patients with AADC deficiency:

> *"He is often irritable and nervous… if he wants to do something and he cannot do it…he becomes irritable"*[51]

Loss of sleep is thought to be a source of immense frustration and distress to patients:

> *"He can't sleep and his eyes are just wide awake, and the frustration is all over his face, you can definitely tell that he has a lot of discomfort."*[51]

Despite this emotional burden, caregivers of patients feel that their child cannot fully communicate their feelings, potentially further exacerbating their level of distress and frustration

> *"He does understand…he recognizes and knows things more than he can communicate."*[51]

> *"She does cry a lot. I think too because not being able to be verbal and communicate and things"*[11]

Taken together, it is reasonable to assume that the severity of AADC deficiency symptoms translates to a very poor quality-of-life for patients, despite the lack of literature on patient-reported outcomes.

B.1.3.6.4. Activities of daily living

Patients with severe AADC deficiency are completely dependent on caregiver support for all aspects of daily living throughout their lifetime#

Severe AADC deficiency significantly impacts motor development, and most children are unable to hold their head up, sit by themselves, stand, or speak over their lifetime. Unable to communicate, many patients are unable to partake in the activities of healthy children, such as go to school, play with toys or even feed themselves.[6,60,62, 13] The limitation of the disease affects all aspects of everyday physical functioning and therefore patients depend entirely on their carers for 24-hour care.[51] Of 38 patients aged 5 years or older who provided data on functional independence for activities of daily living and adaptive behaviour in Pearson *et al.* 2020, 71% (27/38) were classified as "completely dependent".[7]

In a qualitative study on symptoms and impacts of AADC deficiency, caregivers described the severe impact it has on everyday life:

> *"He doesn't have a normal daily life… I can't even imagine what things feel like being him. That's the truth… there are no happy baby moments during the day. The best I hope for is no issues"*[51]

> *"A typical day for her… she can do nothing, the only thing that comforts her are the walks, and well, then we put her on the blanket, we play like a little bit, but all the movements she makes, we are the ones making them"*[11]

As a result of the severely impaired motor and cognitive function, many patients are unable to socially interact with other children:

> *"He can't play with other children, because he can't really walk, he can't hold his head up, so no… he can't actively participate with toddlers his age"*[51]

> *"He cannot attend school every day like the normal children, he plays but also in this case, he plays because I make him play, I sit there with him, because he cannot even raise his arms alone"*[11]

Everyday life is also impacted by the need for frequent healthcare visits. Severe patients with AADC deficiency are subject to frequent hospitalizations and appointments, with a study conducted by Boston Children's Hospital of five families with AADC deficiency describing one ten-year-old patient who attended 234 appointments over two years and one three-year-old visiting 15 different medical specialists.[63] This highlights the challenges for the entire family of a patient living with such a devastating and debilitating condition.

B.1.3.7 Caregiver quality-of-life

Children with AADC deficiency require 24-hour care, causing profound physical, emotional, and financial challenges for family caregivers

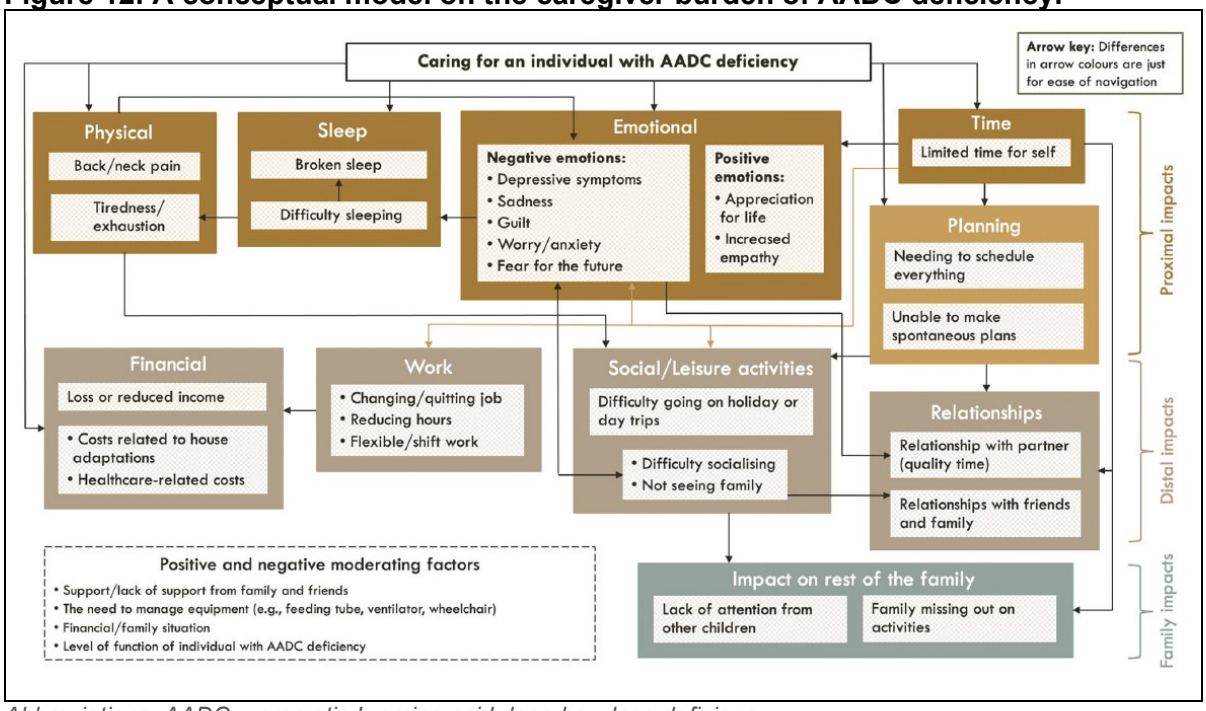
In addition to the patient burden, AADC deficiency has a major physical, emotional and financial impact on families and carers of the patient.[61] Caring for a child with AADC deficiency requires round-the-clock, one-to-one support with all aspects of daily living, including dressing, bathing, eating, and, for many patients, moving.[13] As caregivers spend nearly every waking moment caring for patients with AADC deficiency, it requires most of them to stop or at least reduce their working hours.[13] Behavioural complications of AADC deficiency, which can include excessive crying, irritability and dysphoria (general unease and unhappiness), can also be a great burden to caregivers.[2]

Family caregivers spend an average of 13 hours a day supporting their child with AADC deficiency and a further 15 hours a week on administrative tasks

While there is limited published evidence regarding the QoL of a carer of a child with AADC deficiency, qualitative studies exploring the caregiver burden of AADC deficiency indicate a major impact.[62, 13] In one study, carers reported spending an average of 13 hours (8-20h) per day on practical and emotional care for their child, indicating that most of a carer's daily life is dedicated to the patient, with very little time for themselves. The same caregivers spent an average of 15 hours (7-33h) per week on administrative tasks, including travelling to/attending appointments relating to their child's AADC deficiency.[13] Therefore, due to the severe and wide-varying symptoms of AADC deficiency, carers are required to provide around the clock care for their child.

Figure 12 demonstrates the breadth and depth of detrimental impact that providing full-time care for a patient with AADC deficiency has on a carer. All aspects of a carer's life are negatively impacted.

Figure 12: A conceptual model on the caregiver burden of AADC deficiency.



Abbreviations: AADC = aromatic L-amino acid decarboxylase deficiency
Source: Skrobanski et al., 2021[61]

Caring for a patient with no motor function places caregivers under immense physical strain

Physically, carers are placed under enormous strain by having to look after patients with AADC deficiency. As patients face failure of key motor milestones, carers are required to provide constant physical support in the form of carrying or moving patients. As patients get older through infancy and childhood, their weight will increase, resulting in higher physical demands from the carer. Table 4 demonstrates the disutilities in carers of multiple sclerosis, which, like AADC deficiency, affects a patient's motor functioning. As a patient's motor function worsens, the caregiver burden increases. The impact in AADC deficiency is expected to be even higher than in multiple sclerosis due to the broad range of symptoms associated with the condition.

Table 4: Caregiver disutility values based on patient motor functioning

Motor milestone state	Acaster *et al.*, (2013)
No motor function	0.09
Full head alignment	0.09
Sitting (unaided)	0.03
Stepping (i.e., standing with support)	0.03
Walking with assistance	0.00

Caregiver disutilities derived from carers of patients with multiple sclerosis, as reported in NICE HST2. Abbreviations: HST - Highly specialised technology; NICE - National Institute for Health and Care Excellence. Source: NICE HST2[29]

Caregivers are unable to continue employment or socialise due to the demands of caring for a child with AADC deficiency

As a result of the considerable amount of time spent providing care for patients with AADC deficiency, carers relinquish their own social activities and employment.[61] Caregivers report having very little to no time for themselves, resulting in an impact in their ability to carry out everyday tasks, go to work or socialise.[61] Caregivers of patients with AADC deficiency report the following:

> *"It's pretty much nonstop, so I can't have a social life… so no social life… pretty much no leisure activities"*[61]

> *"My life is schedule[d] minute by minute. I have to plan things, I cannot miss one hour, I panic, I get paranoid, because I have to do this and that"*[61]

> *It's a big commitment and it's a lot and you do need to sacrifice a lot. Free time, socialisation, going out and doing things…I would is say is like the biggest impact has been that lack of spontaneity and having to have a schedule and not being able just to go up and take off and do things without, you know, zero planning*

Furthermore, 75% of carers reported that they stopped working or reduced their working hours in order to take care of their child.[13] In line with this, an analysis of caregiver burden by Boston Children's Hospital showed a consistently high caregiver burden, including the inability to maintain regular employment.[63] This lost or reduced income, along with the associated direct costs of medical tests, treatments and medical insurance and indirect costs of adapting their home or care, causes family financial problems.[61]

Caring for a child with AADC deficiency is emotionally challenging and causes depression, sadness, and anxiety

Caring for a patient with AADC deficiency also causes a substantial burden on the emotional wellbeing of carers and families. Caregivers experience depressive symptoms, sadness and anxiety.[61] It is common for families to miss out on activities and parents are unable to give attention to their other children.[61] The constant care for a child with AADC deficiency means there is limited time for relationships, as reported by caregivers:

> *"We [my husband and I] were quite distant at a physical level and we weren't talking much, we were not on the same track… my concern was not any more a husband and a marriage, I was concentrating on other things"*[61]

> *"It's very difficult, emotionally it's very heavy, psychologically heavy, and what else can I say, and then my life as well, I don't want to be misinterpreted, because in a way, my life has changed, my life it's not the life I wanted to have with my son"*[11]

"The negatives, of course, you don't want to see your child have to struggle…there's been times where I have been super depressed"[11]

Taken together, the considerable amount of time, emotional burden and physical strain involved with caring for a child with severe AADC deficiency is likely to considerably impact carer QoL.

B.1.3.8 Current treatments and unmet need

B.1.3.8.1. Current clinical management of AADC deficiency in the UK

There are no disease-modifying treatments for AADC deficiency and current best supportive care involves multiple symptomatic treatments and specialist visits

There are currently no disease-modifying treatments for AADC deficiency and patient management relies on attempted symptom control.[2] Current management includes an extensive list of medication and multidisciplinary team support from specialists.[2] A recent study exploring the clinical and economic burden of AADC deficiency in the UK found that each patient requires 4–14 different medications and visits 6 different specialists each year.[46]

There are no UK clinical guidelines for AADC deficiency

There are no relevant guidelines on AADC deficiency in the UK, including from the National Institute for Health and Care excellence (NICE), NHS England, or other sources. In addition to no guidance, no treatments are licenced specifically for patients with AADC deficiency, and current best practice is best supportive care (BSC). BSC is highly individualised and includes symptomatic treatments and support from a multidisciplinary team of specialists. BSC aims to address the profound symptoms, issues, comorbidities, and complications associated with the AADC deficiency.[2] Patients are managed with a varying and wide-ranging number of drugs and by a variety of specialists, regardless of severity.[46]

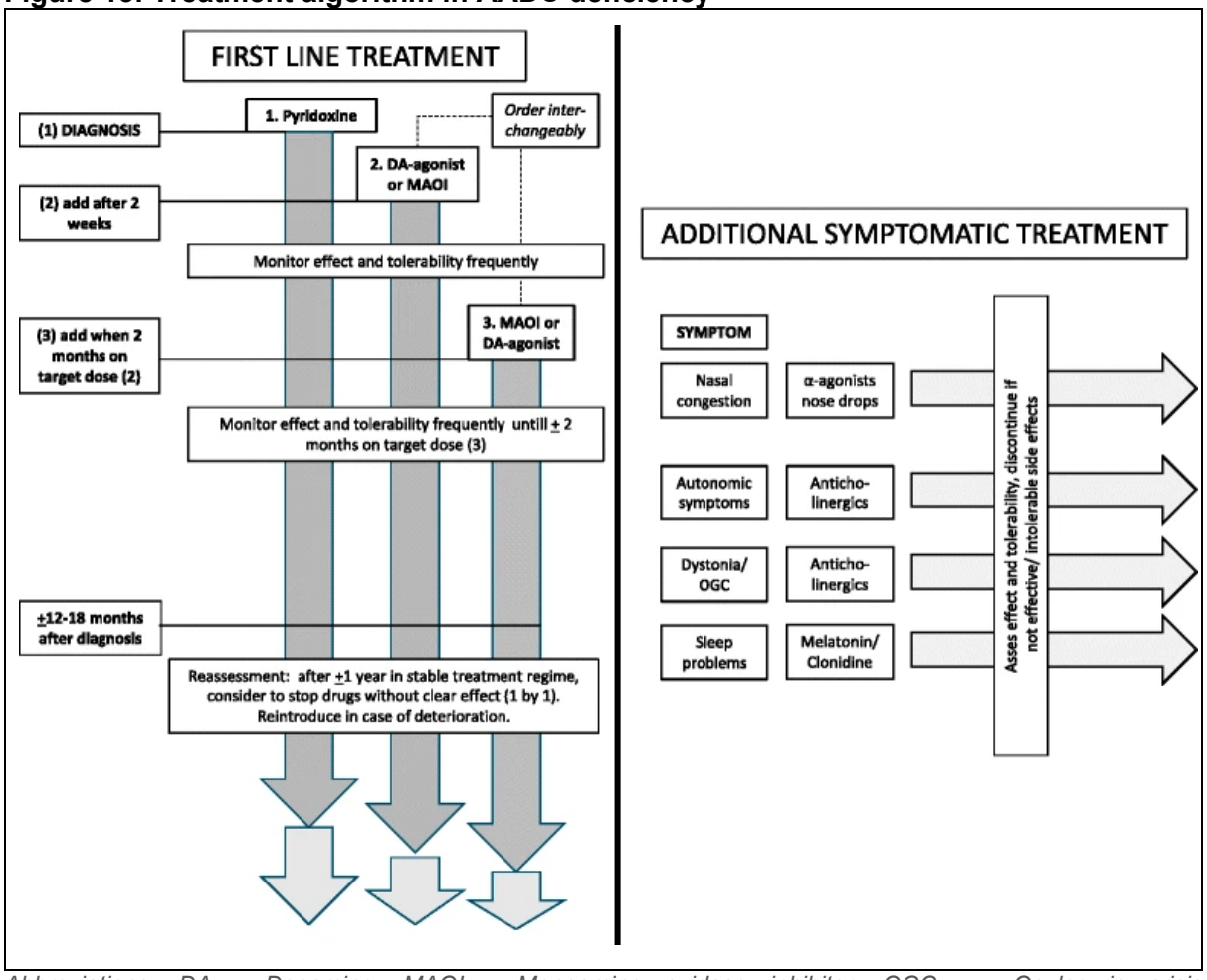
International guidelines rate treatments used in AADC deficiency as having "low" or "very low" quality of evidence supporting their use

In the absence of UK guidance, the current management of patients with AADC deficiency may be informed by a consensus guideline for the diagnosis and treatment of AADC deficiency, developed by the International Working Group on neurotransmitter Related Disorders (iNTD) (Wassenberg *et al.* in 2017).[2] The consensus studied 117 cases of AADC deficiency with 82 severe, 15 mild and 6 moderate cases confirmed.[2] Among the named authors of the guideline are three UK-based experts: Manju Kurian, Simon Heales, and Lisa Flint.[2]

According to the Wassenberg 2017 consensus guidelines, the most commonly used symptomatic treatments for BSC all target the dopamine pathway: dopamine receptor agonists (used to activate postsynaptic dopamine receptors), monoamine oxidase (MAO) inhibitors (prevent the breakdown of dopamine and serotonin), and pyridoxine/pyridoxal phosphate (aimed to increase the activity of the AADC enzyme).[2,46,64] All first-line symptomatic treatments aim to solely manage the symptoms of AADC deficiency and come with numerous side effects.[3,7,46] Despite the use of a range of medications, Wassenberg rated the level of evidence supporting each class of medication as "low" or "very low",[2] and there is currently no approved treatment that directly corrects the underlying cause of the disease.[14]

A summary of the AADC deficiency treatment algorithm proposed in the Wassenberg 2017 consensus guidelines is provided in Figure 13.[2]

Figure 13: Treatment algorithm in AADC deficiency



Abbreviations: DA - Dopamine; MAOI - Monoamine oxidase inhibitor; OGC - Oculogyric crisis
Source: Wassenberg T et al. Orphanet Journal of Rare Diseases 2017[2]

Current best supportive care in the UK requires a high number of treatments and multidisciplinary team support from specialists

In addition to the high number of medications, patients with AADC deficiency on BSC also require a large multidisciplinary team of specialists and a complex coordination of care to

address significant health issues, including developmental delays, infections, orthopaedic and cardiac complications, and other comorbidities. Specialists include paediatric neurologists, gastrointestinal specialists, endocrinologists, orthopaedic surgeons, speech therapists, pulmonologists, and physical and occupational therapists.[2] A recent study exploring the clinical and economic burden of AADC deficiency in the UK found that patients see on average 6 different specialists.[46] The high number of pharmacological and non-pharmacological approaches to managing patients with AADC deficiency emphasises the challenges of caring for patients with this devastating condition.

B.1.3.8.2. Issues and uncertainty with current clinical practice

Current UK practice is limited by the lack of treatment options that address the underlying genetic cause of the disease

There are a number of uncertainties regarding current clinical practice, including those related to diagnosis and treatment.

Diagnosis is often delayed.[2] This is due to the ultra-rare nature of the disease and its wide-ranging symptoms, which mean that clinicians may not have familiarity and may confuse AADC deficiency with other conditions, such as cerebral palsy, motor/movement disorders, or seizure disorders (e.g. epilepsy).[7,46]

There is no formal clinical treatment pathway or best practice for treating patients with AADC deficiency in the UK, and patients are often treated with wide-ranging and a varying number of symptomatic medications. Current best practice for the treatment of AADC deficiency is BSC, which involves symptomatic management as well as multidisciplinary team care to address the complications associated with the disease.[2] The extensive list of medications varies from patient-to-patient, with a UK clinician survey on the clinical and economic burden of AADC deficiency in the UK finding that patients are managed with between 4-14 different medications, regardless of severity, and visit a mean of 6 different specialists each year.[46]

Based on its rarity and the limited literature available, the best practice management of patients is unclear and response to treatment varies widely. In a study by Pearson *et al.* 2020 involving 59 patients with data on treatment effects, at least one dopamine agonist was tried in 83% of patients (49/59), including bromocriptine (46%, 27/59), pramipexole (41%, 24/59), rotigotine (20%, 12/59) and ropinirole (14%, 8/59). Rotigotine was beneficial in 82% of patients (10/12), much higher than the 29% (7/24), 26% (7/27) and 13% (1/8) of patients who benefited from pramipexole, bromocriptine and ropinirole, respectively. The rate of adverse effects associated with the dopamine agonists was 50% with rotigotine and ropinirole, 38% with pramipexole and 30% with bromocriptine and led to discontinuation in 25% of subjects.[7] Thus, there is an unclear benefit-risk profile with current therapies.

Without new treatment approaches, patients with severe AADC deficiency are likely to remain bedbound during their shortened life

Most notably, current management very rarely helps patients with severe AADC deficiency to achieve any motor milestones. According to a natural history database based on published cases of AADC deficiency, only 3% of patients with severe AADC deficiency (i.e. no or poor head control at baseline) achieve any improvement in motor milestones.[8] Patients are likely to remain bedbound with a wide range of severe symptoms for their entire shortened life and are likely to die before they reach adulthood. There is, therefore, a huge unmet need for a disease-modifying treatment that addresses the underlying genetic cause of AADC deficiency.

B.1.3.8.3. Unmet need

There is a clear and urgent need for disease-modifying therapies that address the genetic root cause of AADC deficiency

Given the lack of disease-modifying treatments, patients with severe AADC deficiency face life-long motor and development deficiencies, a severe impact on growth and function, the inability to move or communicate, and the risk of early mortality (within the first decade), with no effective treatment options to significantly impact disease progression. Caregivers are required to provide life-long round-the-clock care, causing profound emotional and physical distress. There is, therefore, a clear, critical, and urgent need for a novel disease-modifying treatment that can address the underlying genetic cause of AADC deficiency.

B.1.3.9 Introduction to eladocagene exuparvovec

Eladocagene exuparvovec is a highly innovative gene-replacement therapy that addresses the genetic cause of AADC deficiency, modifies the disease course, and is the first and only licensed therapy in AADC deficiency

Eladocagene exuparvovec is a single dose gene replacement therapy which is expected to be indicated for the treatment of patients [redacted].[31] It is the first and only licensed treatment that addresses the underlying cause of AADC deficiency.

Eladocagene exuparvovec is a single dose gene replacement therapy consisting of a recombinant adeno-associated virus serotype 2 (AAV2) that contains the human dopa decarboxylase (*DDC*) gene, which encodes the human AADC enzyme.[34] Eladocagene exuparvovec provides a full copy of the *DDC* gene and is therefore anticipated to be effective regardless of the type of genetic mutation.

By delivering a functioning *DDC* gene directly into the brain's putamen, eladocagene exuparvovec restores production of the AADC enzyme, in turn, restoring dopamine production. Dopamine is a key neurotransmitter involved in voluntary motor movements, learning and memory, cognition and emotion.[36] Dopamine is also the precursor of adrenaline and noradrenaline, which can act as both neurotransmitters and hormones within the body,

playing a vital role in the body's fight or flight response.[3] Low levels of adrenaline and noradrenaline can result in anxiety, depression, changes in blood pressure, changes in heart rate, hypoglycaemia, and problems sleeping.[65] Thus, by restoring production of dopamine, eladocagene exuparvovec restores the key health outcomes reliant on dopamine production.

Eladocagene exuparvovec provides clear patient benefits over at least 5 years follow-up according to data from the PTC-AADC-010, -011, and –CU/1601 studies, including:[31]

- **Improved motor function:** Patients treated with eladocagene exuparvovec rapidly and durably improve from having no motor function to achieving key motor milestones, including full head control, sitting unassisted, standing with support, and walking with assistance. Improvements in motor function occur from as early as 3 months and continue beyond 5 years following treatment.[10,31]
- **Reduced OGCs:** There was a sustained reduction in the frequency and duration of OGC following eladocagene exuparvovec.[10,31]
- **Improved cognition and communication:** Treated patients experienced sustained improvements in measures of development, cognition, and language.[10,31]
- **Improved body weight:** Treated patients had weight gains consistent with age- and gender-matched normal children.[31]
- **Reduced floppiness:** The proportion of patients with dystonia, hypotonia, and stimulus-provoked dystonia reduces over time following gene-replacement therapy.[31]
- **Reduced respiratory infections:** The annual rate of respiratory infections decreases following gene-replacement therapy.[31]

The profound and life-changing benefits of eladocagene exuparvovec are best emphasised by observing videos of patients several years after treatment. Please refer to Tai *et al.* (2022)[10] and the EMA Scientific Advisory Group video of patient 311[19] to observe the enormous benefits that eladocagene exuparvovec can offer.

For more information on the clinical benefits of eladocagene exuparvovec, please refer to Section B.2.

B.1.3.10 The new care pathway incorporating eladocagene exuparvovec

B.1.3.10.1. Overview

Eladocagene exuparvovec will transform the pathway of care in the UK

Eladocagene exuparvovec is a step-change and will transform the pathway of care for patients with AADC deficiency. It will be the first treatment that addresses the underlying cause of AADC deficiency and is expected to become the standard of care. The expected number of patients eligible for the use of eladocagene exuparvovec per year is small and the treatment is expected to be administered at 1-2 highly specialised centre(s) with the facilities and technical capabilities to deliver the pre-, peri-, and post-administration care. Therefore, NHS England national commissioning and oversight is essential. In addition, PTC are working to

put in place a comprehensive training and education programme on the preparation, handling, and administration of eladocagene exuparvovec, so that treating surgeons and their teams at accredited treatment centre(s) have the requisite knowledge and experience to deliver this novel therapy.

Eladocagene exuparvovec is expected to be the first treatment that addresses the underlying cause of AADC deficiency, and the first treatment licensed specifically in AADC deficiency. It is therefore anticipated that all patients with AADC deficiency in the UK will be assessed for their eligibility to receive eladocagene exuparvovec. The impact that eladocagene exuparvovec will have on the use of current BSC symptomatic treatments is not yet known but it is expected that patients will receive treatments on an individual basis following eladocagene exuparvovec.

B.1.3.10.2. Pre-administration patient management

The management of patients with AADC deficiency prior to administration of eladocagene exuparvovec will be conducted at specialised centre(s) within England that currently manage patients with AADC deficiency. Patients receiving treatment with eladocagene exuparvovec will be aligned to the final licenced indication (see section B.1.1 for details regarding the indication).

Patients may undergo additional examinations compared to usual clinical practice prior to receiving eladocagene exuparvovec. These additional tests include an MRI evaluation for planning of the stereotactic surgery. Further details of pre-operative tests required prior to the administration of eladocagene exuparvovec are detailed in Section B.3.5.1.1.2.

B.1.3.10.3. Administration of eladocagene exuparvovec

Eladocagene exuparvovec is available in a single-use vial that is stored at -65ºC. Once the date of surgery has been agreed, a qualified pharmacist is required to thaw the product, and administration should begin within 6 hours of thawing.[31]

In line with the SmPC, eladocagene exuparvovec should be administered by a qualified neurosurgeon in a surgical suite under controlled aseptic conditions. Eladocagene exuparvovec is administered by stereotactic surgery and is expected to involve a multidisciplinary team of neurosurgeons, paediatric neurologists, and pharmacists. CT and MRI images may be used to guide the trajectory to the target region.[31,66]

Eladocagene exuparvovec is administered in a single surgical session by bilateral infusion directly into the putamen. It will be the first approved gene therapy to be administered directly into the brain. It is administered to four different sites in the putamen (right and left anterior, right and left posterior) in four equal infusions totalling a dose of $1.8x10^{11}$ vg ($0.45x10^{11}$ vg per

infusion).[31] Administration requires stereotactic surgery,[31] a minimally invasive surgical technique that is widely used in neurosurgery. The procedure requires a SmartFlow cannula and may also involve the use of commercially available systems that provide real-time MRI guidance to ensure eladocagene exuparvovec is delivered to the correct location. The total procedure time is expected to be 6-8 hours.

PTC are working to put in place a comprehensive training and education programme[31,66] on the preparation, handling, and administration of the therapy, so that treating surgeons and their teams at accredited treatment centres have the requisite knowledge and experience to deliver eladocagene exuparvovec.

B.1.3.10.4. Post-administration patient management

Once the patient has received treatment with eladocagene exuparvovec, they require post-operative care and ongoing safety monitoring, provided by a specialist team with expertise in the administration of the therapy and managing AADC deficiency.

Post-operative care includes standard neurosurgical procedures to close the surgical site, followed by a CT scan to confirm there are no post-operative complications (i.e. bleeding) at the sites of infusion.

As per the SmPC,[31] immediately after administration of eladocagene exuparvovec, the patient undergoes a post-operative CT scan to ensure there are no complications (i.e. bleeding). The patient must reside in the vicinity of the hospital where the procedure was performed for at least 48 hours following the procedure, before returning home.

As per the SmPC,[31] post-treatment care should be managed by the referring paediatric neurologist and/or with the neurosurgeon and include at least two follow up visits. The patient will have a first follow up 7 days after surgery to ensure that no complications have developed. A second follow up visit will take place 2 weeks later (i.e. 3 weeks after the surgery) to monitor post-surgical recovery and occurrence of adverse events. Specialist follow-ups continue for the months following the treatment of eladocagene exuparvovec. Patients may undergo additional examinations as part of the post-operative care such as CT scan, PET scan, and lumbar puncture. For further detail around the post-operative costs associated with the administration of eladocagene exuparvovec, see Section B.3.5.1.1.2.

Eladocagene exuparvovec offers a step-change in the treatment pathway of patients with AADC deficiency, enabling the achievement of motor milestones (e.g. full head alignment and sitting) and improvement in other symptoms, such as OGC.[67–69] As a result of an improved prognosis, the care requirements of patients may change over time, but patients are likely to continue to need multidisciplinary management and a tailored, symptom-led approach to care

B.1.4. Equality considerations

PTC Therapeutics does not consider there to be any equality considerations related to the technology. Given the severe and life-shortening nature of the condition, the treatment should be made available to all eligible patients.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted on 23 February 2022 to identify publications related to the clinical efficacy and safety of eladocagene exuparvovec and best supportive care (BSC). The SLR also included searches for publications on (i) cost-effectiveness studies, (ii) utilities, and (iii) cost and resource use outcomes in AADC deficiency (as detailed in Section B.3). The SLR was conducted in line with the University of York Centre for Reviews and Dissemination guidance and the NICE manual published in 2022[70,71].

Relevant publications were identified by searching the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Medline (R) In-Process (Embase interface 1947 to present), Excerpta Medica database (EMBASE), Cochrane Central Register of Controlled Trials (Cochrane library), Centre for Reviews and Dissemination (CRD) HTA Database (1989 to present), CRD National Health Service (NHS) Economic Evaluation Database (EED), ScHARRHUD (2006 to present) and EuroQol database (1970 to present). Please see Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to this NICE appraisal.

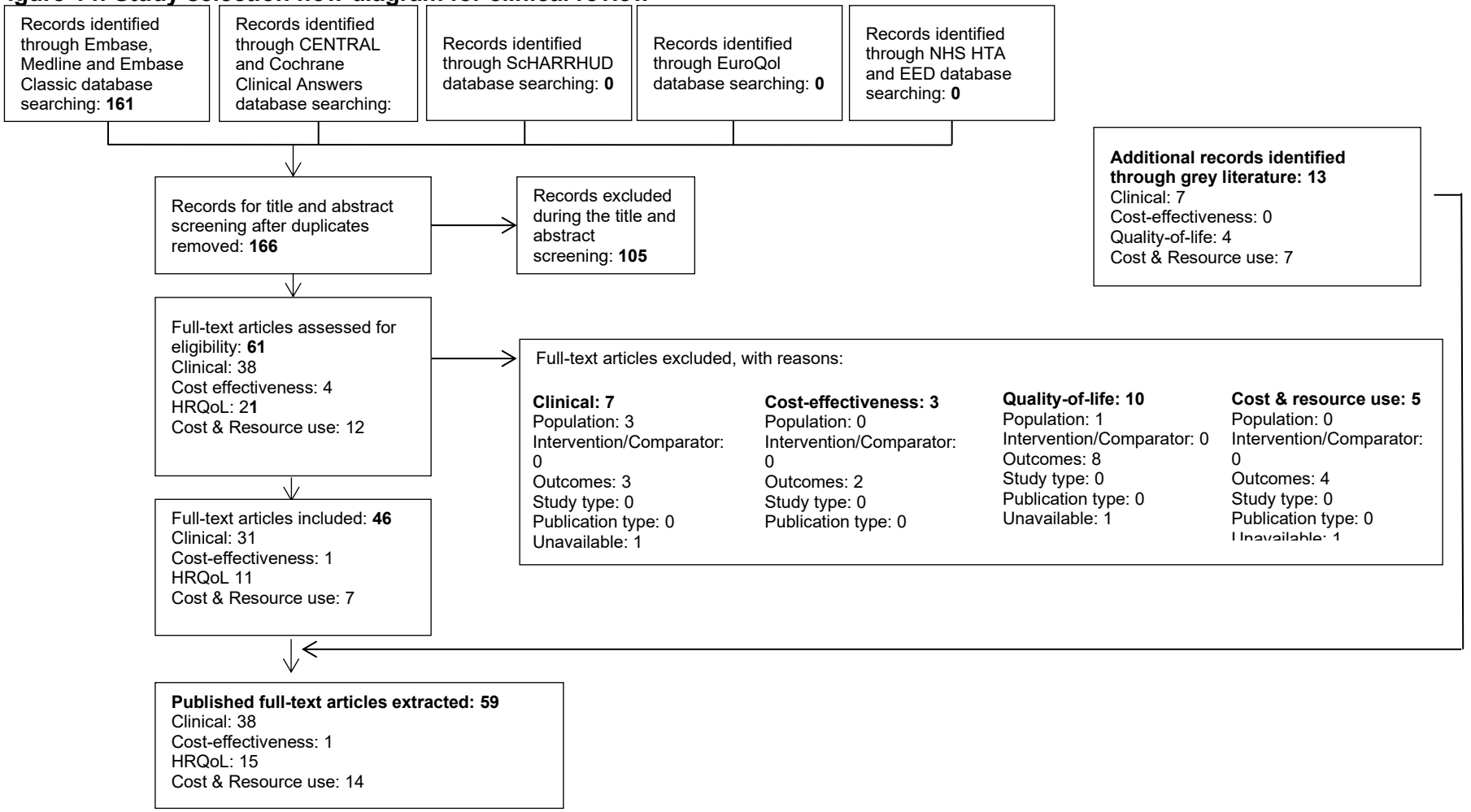
B.2.1.1 Number of published (and unpublished) studies included and excluded at each stage

B.2.1.1.1. Published literature

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram below (Figure 14) summarises the screening of publications through each stage of the SLR resulting in all published literature identified. The database search retrieved 166 unique publications (i.e. once duplicates were removed), of which 105 were excluded at first-pass screening, leaving 61 publications for full-text screening. Of these 61 full-text publications, 46 met the criteria to be included and were extracted. Grey literature searches produced a further 13 publications for data extraction, meaning a total of 59 publications were extracted. Of these, 38 were clinical publications relevant to this submission (See Table 94 in Appendix C for excluded studies and rationale for excluding).

All the clinical publications identified for data extraction in this SLR were non-RCTs. This is expected given that AADC deficiency is extremely rare and there are currently no approved disease-modifying therapies available worldwide. The SLR retrieved 38 publications relating to either eladocagene exuparvovec or best supportive care (BSC) (Table 96). Of these, 23 were related to eladocagene exuparvovec, all of which were based on three clinical trials: AADC-010, AADC-011 and AADC-CU/1601 (Table 42). Eleven of the publications were related to BSC. A further 5 publications report another experimental gene-replacement therapy (adeno-associated virus serotype 2 [AAV2]-hAADC), which is not relevant to this appraisal as it does not have a marketing authorisation. Some of the papers reported outcomes for both BSC and the other experimental gene-replacement therapy.

Figure 14: Study selection flow diagram for clinical review



Please note: The total number of publications in each box does not equal the summation of the 4 review questions below it due to some publications containing information for >1 review question

B.2.1.1.2. Unpublished literature

Furthermore, to the database and grey literature searching for published evidence, sources of unpublished clinical data relevant to this appraisal were identified from internal data on file at PTC and are included in this submission.

The literature search for unpublished studies identified three clinical study reports (CSRs) for the three clinical trials that have been conducted assessing eladocagene exuparvovec gene-replacement therapy in patients with AADC deficiency.

B.2.2. List of relevant clinical effectiveness evidence

The SLR retrieved 23 clinical effectiveness publications reporting on eladocagene exuparvovec, all of which relate to three open-label, single-arm, non-RCTs (Appendix D) corresponding to the following unpublished CSRs:

- AADC-010 (phase I/II): NCT01395641[18]
- AADC-011 (phase II): NCT02926066 [17]
- AADC-CU/1601: Compassionate use study[16]

For completeness and consistency, the primary data sources for eladocagene exuparvovec in this NICE submission are the clinical study reports for AADC-010, AADC-011 and AADC-CU/1601, while publications related to the studies are used as supporting information (please see Table 42 for an overview of the trials used in this submission). All three trials (AADC-010, AADC-011, AADC-CU/1601) were used to support the European Medicines Agency (EMA) marketing authorisation for eladocagene exuparvovec.

In this submission, the latest CSR is used for each study. Please note that the CSR for the AADC-011 study is currently being updated with additional analyses as part of the EMA regulatory appraisal. The final version was not available at the time of the NICE submission deadline. In this submission, a draft version of the CSR is therefore used for the AADC-011 study.[17]

Table 6 and Table 7 detail the clinical effectiveness evidence for AADC-010, AADC-011 and AADC-CU/1601, respectively. It should be noted that AADC-011 investigated two doses of eladocagene exuparvovec: $1.8x10^{11}$ vg and $2.4x10^{11}$ vg. The higher dose was selected for logistical reasons to remove a dilution step and simplify the administration of the study drug. The EMA considered the two doses to be equivalent in terms of safety and efficacy (as reflected in the SmPC)' and, therefore to maximise the use of the data available, the full dataset across both doses are included in this appraisal.[14]

Appendix D provides a full list of the 23 relevant publications reporting clinical effectiveness data for eladocagene exuparvovec and how each publication corresponds to each of the three clinical studies. The most recent publication related to eladocagene exuparvovec clinical studies is Tai *et al.*, 2022.[68]

Table 5: List of relevant published clinical effectiveness evidence for eladocagene exuparvovec treatment[16 ,18,17,72,73]

Primary source	Population	Intervention	Primary outcomes	Secondary outcomes
AADC-010 (phase I/II; NCT01395641): **Clinical study report**[18]	Children aged 2+ years with AADC deficiency	Eladocagene exuparvovec: total dose of 1.8×10^{11} vg in one operating session (n=10)	Proportion of patients achieving motor milestones* at 5-year timepoint, as measured using the PDMS-2	The secondary efficacy endpoints were: • Raw scores for the PDMS-2 total and subscales • Raw scores for the Alberta Infant Motor Scale (AIMS) total and subscales • Raw scores for the Bayley Scales of Infant Development – Third Edition (Bayley-III) total and subscales • Change from baseline in body weight • Neurologic examination findings with respect to muscle tone (ie, floppiness), OGC episodes, dystonia, muscle power, and deep tendon reflex (DTR) response
AADC-011 (phase II; NCT02926066): **Clinical study report**[17]	Children aged 2 - 6 years with AADC deficiency	1.8×10^{11} vg dose given to patients 3 years and older (n=3) 2.4×10^{11} vg dose given to patients less than 3 years old (n=9). Total (n=12)	Proportion of patients achieving motor milestones* at 1-year timepoint, as measured using the PDMS-2	The secondary efficacy endpoints were: • Raw scores for the PDMS-2 total and subscales • Raw scores for the AIMS total and subscales • Raw scores for the Bayley-III total and subscales • Change from baseline in body weight • Neurologic examination findings with respect to muscle tone (ie, floppiness), OGC episodes, dystonia, muscle power, and deep tendon reflex (DTR) response
AADC-CU/1601 (Compassionate use study): **Clinical study report**[16]	Children aged 2+ years with AADC deficiency	Eladocagene exuparvovec: total dose of 1.8×10^{11} vg administered during a single session (n=8)	The proportion of patients who achieved key motor milestones at the 60-month timepoint, as assessed using the PDMS-2 scale. The proportion of patients at each motor milestone at Month 12 and 24 was provided as supportive analyses. Motor milestones were defined as follows: • Full head control: The patient was considered successful on this task only if he/she achieved a score of 2 on Item #10 of the Stationary (gross motor) subscale by sitting supported at his/her hips and holding his/her head aligned while	The secondary efficacy endpoints were: • Raw scores for the PDMS-2 total and subscales (Month 60) • Raw scores for the AIMS total and subscales (Month 60) • Raw scores for the CDIIT whole test and subtests (Month 60) • Change from baseline in body weight (collected at each visit) Neurological examination findings with respect to muscle tone (ie, floppiness), OGC episodes,

			rotating his/her head to follow a toy for 8 seconds. • Sitting unassisted: A patient was considered successful in sitting unassisted only if he/she scored a maximum score of 2 on Item #14 of the Stationary subtest, which required the patient to sit without support and maintain balance while in a sitting position for 60 seconds. • Stand with support: A patient was considered successful at stepping while standing with support only if he/she achieved a maximum score of 2 on Item #28 of the Locomotion (gross motor) subscale, which required the patient to take at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk, consistent with, standing with support. Walk with assistance: A patient was considered successful only if he/she scored a maximum score of 2 on Item #34 of the Locomotion (gross motor) subscale, which required the patient to walk at least 8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.	dystonia, muscle power, and deep tendon reflex response (every month for the first year of follow-up)

** Motor milestones were defined as follows:*

1. *Full head control is defined as: (a) Score criteria 1 (newly emerging): Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 seconds. (b) Score criteria 2 (mastery): Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds.*
2. *Sitting unassisted is defined as: (a) Score criteria 1 (newly emerging): sitting without support and maintain balance while in a sitting position for 30 to 59 seconds', (b) Score criteria 2 (mastery): sitting without support and maintain balance while in a sitting position for 60 seconds*
3. *Standing with support is defined as: (a) Score criteria 1 (newly emerging): Taking 2 to 3 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk (b) Score criteria 2 (mastery): Taking at least 4 alternating steps, either in place or forward motion, with the evaluator's hands around the child's trunk.*
4. *Walking with assistance is defined as: (a) Score criteria 1 (newly emerging): Walking 4 to 7 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands. (b) Score criteria 2 (mastery): Walking ≥8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.*

Source: Clinical study reports and statistical analysis reports for AADC-CU/1601, AADC-010 and AADC-011.

Abbreviations: AADC– Aromatic L-amino acid decarboxylase; AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AAV2 - Anti-adeno-associated virus serotype 2; AE – Adverse event; AIMS – Alberta Infant Motor Scale; Bayley-III – Bayley Scales of Infant Development 3rd edition: CDIIT – Comprehensive Developmental Inventory for Infants and Toddlers; F-DOPA - L-6-fluoro-3, 4-dihydroxyphenylalnine; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; OGC – Oculogyric crises; PDMS-2 – Peabody Developmental Motor Scale 2nd edition; PET – Positron emission tomography; TEAEs – Treatment-emergent adverse events

Table 6: AADC-010 - Clinical effectiveness evidence

Study	AADC-010
Study design	Phase I/II: Open-label, single-arm
Population	Children aged ≥2 years with AADC deficiency (n=10): • Confirmed diagnosis of AADC deficiency, including characteristic CSF neurotransmitter metabolite profile or >1 mutation in DDC gene. • Age >2 years or head circumference big enough for surgery
Intervention(s)	Eladocagene exuparvovec: total dose of $1.8x10^{11}$ vg (n=10)
Comparator(s)	No comparator due to ethical reasons and rarity of the disease. Comparison against a natural history control group.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	• Proportion of patients achieving key motor milestones at month 60 using PDMS-2 total and subscale scores. • Raw scores for the PDMS-2 total and subscales • Raw scores for the AIMS total and subscales • Raw scores for the Bayley Scales of Infant Development – Third Edition (Bayley-III) total and subscales • Change from baseline in body weight • Anti-adeno-associated virus serotype 2 (AAV2) optical density (OD) values • Change from baseline in the neurotransmitter metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) • Change from baseline in positron emission tomography (PET • Putaminal-specific L-6-[F] fluoro-3,4-dihydroxyphenylalnine (F-DOPA) PET Uptake • Mortality • All adverse effects
All other reported outcomes	Not applicable

Abbreviations: AIMS – Alberta Infant Motor Scale; CSF – cerebrospinal fluid; N/A – Not available; OGC – Oculogyric crises; PDMS-2 – Peabody Developmental Motor Scale 2nd edition
Source: AADC-010 CSR[18]

Table 7: AADC-011 - Clinical effectiveness evidence

Study	AADC-011
Study design	Phase IIb: Open-label, single-arm
Population	Children aged 2-6 years with AADC deficiency (n=12): • Confirmed diagnosis of AADC deficiency, including characteristic CSF neurotransmitter metabolite profile or >1 mutation in DDC gene • Aged >2 years or head circumference big enough for surgery
Intervention(s)	Eladocagene exuparvovec $1.8x10^{11}$ vg dose given to patients 3 years and older (n=3) Eladocagene exuparvovec $2.4x10^{11}$ vg dose given to patients less than 3 years old (n=9)
Comparator(s)	No comparator due to ethical reasons and rarity of the disease. Comparison against a natural history control group.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	• Proportion of patients achieving key motor milestones at month 12 using PDMS-2 total and subscale scores. • Raw scores for the PDMS-2 total and subscales • Raw scores for the Alberta Infant Motor Scale (AIMS) total and subscales • Raw scores for the Bayley Scales of Infant Development – Third Edition (Bayley-III) total and subscales • Change from baseline in body weight • Neurologic examination findings with respect to muscle tone (ie, floppiness, OGC episodes, dystonia, muscle power, and deep tendon reflex (DTR) response • Anti-adeno-associated virus serotype 2 (AAV2) optical density (OD) values • Change from baseline in the neurotransmitter metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) • Change from baseline in positron emission tomography (PET • Putaminal-specific L-6-[F] fluoro-3,4-dihydroxyphenylalnine (F-DOPA) PET Uptake • Mortality • All adverse effects
All other reported outcomes	Not applicable

Abbreviations: AIMS – Alberta Infant Motor Scale; N/A – Not available; OGC – Oculogyric crises; PDMS-2 – Peabody Developmental Motor Scale 2nd edition
Source: AADC-011 CSR[17]

Table 8: AADC-CU/1601 - Clinical effectiveness evidence

Study	AADC-CU/1601
Study design	AADC-CU: Compassionate use, open-label AADC-1601: Observational Single arm
Population	Children aged ≥2 years with AADC deficiency (n=8): • Confirmed diagnosis of AADC deficiency, including characteristic CSF neurotransmitter metabolite profile or mutation in DDC gene • Aged >2 years
Intervention(s)	Eladocagene exuparvovec: total dose of 1.8×10^{11} vg (n=8)
Comparator(s)	No comparator due to ethical reasons and rarity of the disease. Comparison against a natural history control group.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	• Proportion of patients achieving key motor milestones at month 60 using PDMS-2 total and subscale scores. • Raw scores for PDMS-2 total and subscales (Month 60) • Raw scores for the AIMS total and subscales (Month 60) • Raw scores for CDIIT whole test and subtests (Month 60) • Change from baseline in body weight (at each visit) • Anti-adeno-associated virus serotype 2 (AAV2) optical density (OD) values • Change from baseline in the neurotransmitter metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) • Change from baseline in positron emission tomography (PET • Putaminal-specific L-6-[F] fluoro-3,4-dihydroxyphenylalnine (F-DOPA) PET Uptake • Mortality • All adverse effects
All other reported outcomes	Not applicable

Abbreviations: AIMS – Alberta Infant Motor Scale; CDIIT – Comprehensive Developmental Inventory for Infants and Toddlers; CSF – cerebrospinal fluid; N/A – Not available; OGC – Oculogyric crises; PDMS-2 – Peabody Developmental Motor Scale 2nd edition
Source: AADC-CU/1601 CSR[16]

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Eladocagene exuparvovec has been investigated in three single-arm studies with similar design

Given the ultra-rare nature of AADC deficiency, the clinical trials supporting eladocagene exuparvovec are all single-arm studies: AADC-010 (Phase I/II), AADC-011 (Phase II) and AADC-CU/1601 (compassionate use). Table 9, Table 10 and Table 11 summarise the methodology for the AADC-010, AADC-011 and AADC-CU/1601 trials, respectively.

The three studies (AADC-010, AADC-011 and AADC-CU/1601) cover a sample of 10, 12 and 8 patients, respectively. AADC-010 and AADC-CU/1601 have a median of 5 years of efficacy and safety follow-up data, whilst AADC-011 has 1 year of follow-up data. Patients were followed up at months 3, 6, 9 and 12, with 6- monthly follow ups thereafter for AADC-CU/1601 and AADC-010. It should be noted that two patients in the AADC-011 study, both treated with the higher dose, were not able to attend Month 12 follow-up visits due to the COVID-19 pandemic.

In AADC-CU/1601 and AADC-010, all patients received a 1.8×10^{11} vg dose of eladocagene exuparvovec. In AADC-011, 3 patients received $1.8x10^{11}$ vg and 9 patients received a 2.4×10^{11} vg dose of eladocagene exuparvovec. The higher dose was selected for logistical reasons to remove a dilution step and simplify the administration of the study drug. The EMA considered the two doses to be equivalent in terms of safety and efficacy.

Primary and secondary endpoints across the three studies were similar. The primary endpoint across all three studies was key motor milestone achievement measured based on PDMS-2 scores. Secondary endpoints across the three studies included PDMS-2 raw scores, AIMS total and subscale scores, and CDIIT and Bayley-III total and subscale scores. Safety endpoints across all three trials include a full record of all TEAEs, neurological examination findings, and viral shedding.

Table 9: AADC-010: summary of methodology[18,72]

Study name	A phase 1/2 clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC
Objective	To understand if the expression of hAADC gene transferred by AAV2 vector may facilitate the conversion from L-DOPA to dopamine to improve the motor function of patients To ensure the safety of hAADC gene transfer by AAV2 vector for children with AADC deficiency
Location	Taiwan
Design	Phase I/II: Open-label, single-arm
Duration of study	Complete: 5 years
Patient population	Children aged 2+ with AADC deficiency (n=10): • Confirmed diagnosis of AADC deficiency, including characteristic CSF neurotransmitter metabolite profile or >1 mutation in DDC gene. • Age >2 years or had a head circumference big enough for surgery
Sample size	N = 10
Inclusion criteria	Patients were included in AADC-010 if all the following inclusion criteria were fulfilled: 1. Confirmed diagnosis of AADC, including cerebrospinal fluid analysis to show reduced levels of neurotransmitter metabolites, HVA and 5-HIAA, and higher L-DOPA, together with more than 1 mutation within AADC gene 2. Classical clinical characteristics of AADC deficiency, such as oculogyric crises, hypotonia, and developmental retardation 3. 2+ years of age or a head circumference big enough for surgery
Exclusion criteria	Patients were excluded from the AADC-010 study for any of the following reasons: 1. Significant brain structure abnormality 2. Any health or neurological concerns that may have increased the risk of surgery. The investigator had the right to evaluate the feasibility of a patient for this study based on his or her health condition. 3. Anti-AAV2 neutralizing antibody titre >1200-fold or an enzyme-linked immunosorbent assay (ELISA) OD >1 4. Taking any medications that may affect the study
Intervention(s)	Eladocagene exuparvovec: total dose of 1.8×10^{11} vg in one operating session (n=10)
Baseline differences	See full details of baseline characteristics in Table 12.
Follow up	Patients were followed every 3 months for safety and efficacy assessments through the first year after treatment. The initial planned observation period was 1 year; however, patients voluntarily returned every 6 months to complete developmental tests and adverse event (AE) reporting. • All subjects (100%) followed-up through month 12, and 9 subjects completed follow-up through month 24. The mean duration of follow-up was 52.3 months. • Five subjects (50.0%) had 60 months or more of long-term follow-up. • One patient (10%) was withdrawn between month 12 and month 24 as per investigator decision, due to having influenza B, and died after 12.2 months of follow-up.
Statistical tests	Primary efficacy endpoint: Number and proportion of patients achieving each key motor milestone were computed at 2 years post-gene-replacement therapy. One-sided Exact Binomial Tests were used to test null hypothesise for head control, sitting unassisted and standing with support. Secondary efficacy endpoint: The PDMS-2, AIMS, and Bayley-III were completed at baseline at each time point. Summary statistics were computed on the raw and change from baseline (CFB) scores by time point for each total score and/or subscale score. Each total score and subscale score was also evaluated by a

	repeated measures analysis using SAS PROC MIXED with fixed effects terms for time point, age at gene-replacement therapy (in months), and baseline score.
Primary outcomes	**Primary efficacy endpoints:** The proportion of patients achieving key motor milestones*, measured using the Peabody Developmental Motor Scales – Second Edition (PDMS-2) at the 5-year timepoint.
Secondary outcomes (including scoring methods and timings of assessments)	**Secondary efficacy endpoints:** • Raw scores for the PDMS-2 total and subscales (month 60) • Raw scores for the Alberta Infant Motor Scale (AIMS) total and subscales (month 60) • Raw scores for the Bayley Scales of Infant Development – Third Edition (Bayley-III) total and subscales (month 60) • Change from baseline in body weight (month 12) • Neurologic examination findings with respect to muscle tone (ie, floppiness), OGC episodes, dystonia, muscle power, and deep tendon reflex (DTR) response (month 12)
Safety endpoints	• All treatment-emergent adverse events • Neurologic examination findings (excluding muscle tone, OGC episodes, dystonia, muscle power, and DTR response) • Viral shedding

** Motor milestones were defined as follows:*

1. *Full head control is defined as:*
   a. *Score criteria 1 (newly emerging): Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 seconds.*
   b. *Score criteria 2 (mastery): Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds.*
2. *Sitting unassisted is defined as:*
   a. *Score criteria 1 (newly emerging): sit without support and maintain balance, while sitting, for 30-59 secs*
   b. *Score criteria 2 (mastery): sitting without support and maintain balance, while sitting, for 60 seconds*
3. *Standing with support is defined as:*
   a. *Score criteria 1 (newly emerging): Taking 2 to 3 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk*
   b. *Score criteria 2 (mastery): Taking at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk.*
4. *Walking with assistance is defined as:*
   a. *Score criteria 1 (newly emerging): Walking at 4 to 7 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.*
   b. *Score criteria 2 (mastery): Walking at least 8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.*

Source: Clinical study report and statistical analysis report for AADC-010.

Abbreviations: AADC– Aromatic L-amino acid decarboxylase; AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AE – Adverse event; AIMS – Alberta Infant Motor Scale; CFB – Change from baseline; CI – Confidence interval; CIs – Confidence intervals; CNS – Central nervous system; CSF – Cerebrospinal fluid; DTR – Deep tendon reflex; ELISA - Enzyme-linked immunosorbent assay; hAADC - Human aromatic L-amino acid decarboxylase; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; L-DOPA - L-3, 4-dihydroxyphenylalanine; OGC – Oculogyric crises; PD – Pharmacodynamic; PDMS-2 – Peabody Developmental Motor Scale 2nd edition; PET – Positron emission tomography; OD – Optical density; TEAE – Treatment-emergent adverse events

Table 10: AADC-011: Summary of methodology[17,73]

Study name	A clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC - an expansion
Objective	To evaluate the safety and efficacy of intraputaminal infusion of eladocagene exuparvovec in children with AADC deficiency for a period of up to 1 year after study drug administration to: • give those patients who were not enrolled in the Phase 1/2 trial (i.e. AADC-010) an opportunity for treatment • increase experience in gene-replacement therapy for AADC deficiency • increase the dosage slightly in patients younger than 3 years of age
Location	Taiwan
Design	Phase IIb: Open-label, single-arm
Duration of study	Complete Length of trial: 1 years
Patient population	Children aged 2 - 6 with AADC deficiency (n=12): Confirmed diagnosis of AADC deficiency, including characteristic CSF neurotransmitter metabolite profile or >1 mutation in DDC gene Aged >2 years or had a head circumference big enough for surgery
Sample size	N = 12
Inclusion criteria	Patients were included in the AADC-011 study if all the following inclusion criteria were fulfilled: 1. Confirmed diagnosis of AADC deficiency, such as a CSF analysis showing decreased levels of HVA, 5-HIAA and elevated L-DOPA levels, or the presence of at least 1 AADC gene pathologic mutation. 2. Classical clinical characteristics of AADC deficiency, such as oculogyric crisis, hypotonia, and developmental retardation. 3. 2+ years of age or had a head circumference big enough for surgery. 4. Not older than 6 years old (72 months) prior to being treated with the study drug.
Exclusion criteria	Patients were excluded from the AADC-011 study for any of the following reasons: 1. Significant brain structure abnormality as determined by the investigator. 2. Any health or neurological concerns that may have increased the risk of surgery. The investigator had the right to evaluate the feasibility of a patient for this trial based on his or her health condition. 3. Anti-AAV2 neutralizing antibody titre >1200-fold or an ELISA OD >1. 4. Taking any medications that may affect the outcome of the trial.
Intervention(s)	Eladocagene exuparvovec $1.8x10^{11}$ vg given to patients 3 years and older (n=3) Eladocagene exuparvovec $2.4x10^{11}$ vg given to patients less than 3 years old (n=9)
Baseline differences	See full details of baseline characteristics in Table 12.
Follow up	Patients were monitored for safety and efficacy assessments through the first year of treatment at 5 post-surgical follow-up visits (Day 7, Month 3, Month 6, Month 9 and Month 12). No patients withdrew or were lost to follow-up.
Statistical tests	Primary efficacy endpoint: The number and proportion of patients achieving each key motor milestone were computed at month 12. Due to the limited number of patient data at the time of analysis, no formal statistical hypothesis was tested. Medical history of patients enrolled in this study was evaluated for the achievement of these milestones prior to gene-replacement therapy. Secondary efficacy endpoint: The PDMS-2, AIMS, and Bayley-III were completed at baseline, month 3, month 6, month 9 and month 12. Summary statistics were computed on the raw and change from baseline (CFB) scores by time point for each total score and/or subscale score. Each total score and subscale score was also evaluated by a repeated measures analysis using SAS PROC MIXED with fixed effects terms for time point, age at gene-replacement therapy (in months), and baseline score.
Primary outcomes	**Primary efficacy endpoints:** Proportion of patients achieving key motor milestones* at the 1-year timepoint, as measured using the Peabody Developmental Motor Scales – Second Edition (PDMS-2).

Secondary outcomes	**Secondary efficacy endpoints:** • Raw scores for the PDMS-2 total and subscales (month 12) • Raw scores for the AIMS total and subscales (month 12) • Raw scores for the Bayley Scales of Infant Development – Third Edition (Bayley-III) total and subscales (month 12) • Change from baseline in body weight (month 12) • Neurologic examination findings with respect to muscle tone (ie, floppiness), OGC episodes, dystonia, muscle power, and deep tendon reflex) response (month 12) **Immunogenicity endpoints**: • Anti-AAV2 optical density values (12 months) **Pharmacodynamic endpoints:** • Change from baseline in neurotransmitter metabolites HVA and 5-HIAA in CSF (12 months) • Change from baseline in PET imaging of putaminal-specific F-DOPA PET uptake (12 months)
Safety endpoint	• All treatment-emergent adverse events • Neurologic examination findings (excluding muscle tone, OGC episodes, dystonia, muscle power, and deep tendon reflex response) • Viral shedding

** Motor milestones were defined as follows:*

1. *Full head control is defined as:*
   a. *Score criteria 1 (newly emerging): Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 seconds.*
   b. *Score criteria 2 (mastery): Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds.*
2. *Proportion of patients able to sit unassisted, measured by PDMS-2. Sitting unassisted is defined as:*
   a. *Score criteria 1 (newly emerging): sit without support and maintain balance, while sitting, for 30-59 secs*
   b. *Score criteria 2 (mastery):): sit without support and maintain balance, while sitting, for 60 seconds*
3. *Proportion of patients able to stand with support, measured by PDMS-2. Standing with support is defined as:*
   a. *Score criteria 1 (newly emerging): Taking 2 to 3 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk*
   b. *Score criteria 2 (mastery): Taking at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk.*
4. *Proportion of patients able to walk with assistance, measured by PDMS-2. Walk with assistance defined as:*
   a. *Score criteria 1 (newly emerging): Walking at 4 to 7 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.*
   b. *Score criteria 2 (mastery): Walking at least 8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.*

Source: Clinical study report and statistical analysis report for AADC-011.

Abbreviations: AADC– Aromatic L-amino acid decarboxylase; AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AIMS – Alberta Infant Motor Scale; CFB – Change from baseline; CI – Confidence interval; CIs – Confidence intervals; CSF – Cerebrospinal fluid; DTR – Deep tendon reflex; ELISA - Enzyme-linked immunosorbent assay; F-DOPA - L-6-fluoro-3, 4-dihydroxyphenylalnine; hAADC - Human aromatic L-amino acid decarboxylase; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; PDMS-2 – Peabody Developmental Motor Scale 2nd edition; PET – Positron emission tomography; OD – Optical density; OGC – Oculogyric crises; TEAE – Treatment-emergent adverse events

Table 11: AADC-CU/1601: Summary of methodology[16]

Study name	AADC-CU/1601: Compassionate use treatment with eladocagene exuparvovec in patients with AADC deficiency
Objective	AADC-CU: To evaluate the safety and long-term benefits of administration of the hAADC gene with the AAV2 vector to patients with AADC deficiency. AADC-1601: To collect data from patients with AADC deficiency who received humanitarian assistance treatment following AAV2-hAADC administration via intraputaminal injection, and to observe the safety and efficacy for a period of up to 60 months (5 years) after administration of eladocagene exuparvovec.
Location	Taiwan
Design	AADC-CU: Compassionate use, open-label AADC-1601: Observational Single arm
Duration of study	5 years
Patient population	Children aged 2+ with AADC deficiency (n=8): • Confirmed diagnosis of AADC deficiency, including characteristic CSF neurotransmitter metabolite profile or mutation in DDC gene • Aged >2 years
Sample size	N = 8
Inclusion criteria	Patients were included in AADC-CU/1601 if all the following criteria were fulfilled: 1. Confirmed diagnosis of AADC deficiency, documented by CSF analysis of neurotransmitter metabolites HVA and 5-HIAA and confirmed by enzyme activity test or screening of AADC gene mutation 2. Classical clinical characteristics of AADC deficiency, such as oculogyric crises, hypotonia, and developmental retardation 3. 2+ years of age
Exclusion criteria	Patients were excluded in AADC-CU/1601 if all the following criteria were fulfilled: 1. Any health or neurological concerns that may have increased the risks associated with surgery. 2. Taking any medications that may affect the trial. 3. Severe allergic reaction to the components of the vector preparation/solution used in the preparation of vector.
Intervention	Eladocagene exuparvovec: total dose of 1.8×10^{11} vg (n=8)
Baseline differences	See full details of baseline characteristics in Table 12.
Follow-up	Under the AADC-CU treatment plan, patients were encouraged to complete the voluntary safety follow-up visits but were not obligated to do so. • The majority of patients (n=6) completed the study through Month 60. The mean (standard deviation) duration of follow-up was 62.5 months (2.70 months) (range: 59.9 to 68.3 months). • 100% of patients (n=8) completed visits through Month 12 and 24. Two patients (25%) did not return for voluntary assessments after Month 24, both due to inability to attend the Month 60 visit.
Statistical tests	The primary efficacy endpoints of study AADC-CU/1601 were defined in the SAP as the proportion of patients who: 1) achieved full head control, 2) were able to sit unassisted, 3) were able to stand with support, and 4) were able to walk with

	assistance, as measured using PDMS-2 at 60 months post-gene-replacement therapy. The following tests were conducted on the primary efficacy endpoint milestone data at the 60-month timepoint under a sequential gatekeeping procedure, using a one-sample exact test at a one-sided α=0.025 level of significance: 1. H0: pHC = p0(HC) vs. H1: pHC >p0(HC) 2. H0: pSU = p0(SU) vs. H1: pSU >p0(SU) 3. H0: pSS = p0(SS) vs. H1: pSS >p0(SS) 4. H0: pWA = p0(WA) vs. H1: pWA >p0(WA), where pHC is the proportion of subjects achieving full head control, pSU is the proportion of subjects able to sit unassisted, pSS is the proportion of subjects able to stand with support, and pWA is the proportion of subjects able to walk with assistance. Under the sequential gatekeeping procedure, the hypotheses for head control were tested first, and if the null was rejected, then the hypothesis for sitting unassisted was tested. The process continued until one of the primary endpoints failed to reject its respective null hypothesis or until the fourth set of hypotheses had been tested.
Primary outcomes	**Primary efficacy endpoints:** The proportion of patients who achieved key motor milestones* at the 60-month timepoint, as assessed using the PDMS-2 scale. The proportion of patients at each motor milestone at Month 12 and 24 was provided as supportive analyses.
Secondary outcomes	**Secondary efficacy endpoints:** • Raw scores for the PDMS-2 total and subscales (Month 60) • Raw scores for the AIMS total and subscales (Month 60) • Raw scores for the CDIIT whole test and subtests (Month 60) • Change from baseline in body weight (collected at each visit) • Neurological examination findings with respect to muscle tone (i.e., floppiness), OGC episodes, dystonia, muscle power, and deep tendon reflex response (every month for the first year of follow-up)
Safety endpoints	**Safety endpoints** • All TEAEs (from surgery start time to Month 60) • Neurological exam findings (excluding muscle tone, OGC, dystonia, muscle power, and DTR response), collected monthly for the first year of follow-up. • Viral shedding

** Motor milestones were defined as follows:*

1. *Full head control: The patient was considered successful on this task only if he/she achieved a score of 2 on Item #10 of the Stationary (gross motor) subscale of the PDMS-2 scale by sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds.*
2. *Sitting unassisted: A patient was considered successful in sitting unassisted only if he/she scored a maximum score of 2 on Item #14 of the Stationary subscale of the PDMS-2 scale, which required the patient to sit without support and maintain balance while in a sitting position for 60 seconds.*
3. *Stand with support: A patient was considered successful at stepping while standing with support only if he/she achieved a maximum score of 2 on Item #28 of the Locomotion (gross motor) subscale of the PDMS-2 scale, which required the patient to take at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk, consistent with standing with support.*
4. *Walk with assistance: A patient was considered successful only if he/she scored a maximum score of 2 on Item #34 of the Locomotion (gross motor) subscale of the PDMS-2 scale, which required the patient to walk at least 8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.*

Source: Clinical study report for AADC-CU/1601

Abbreviations: AADC– Aromatic L-amino acid decarboxylase; AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AIMS – Alberta Infant Motor Scale; CDIIT – Comprehensive Developmental Inventory for Infants and Toddlers; CSF – Cerebrospinal fluid; DTR – Deep tendon reflex; ; hAADC - Human aromatic L-amino acid decarboxylase; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; IEC – Independent ethics committee; IRB – Institutional review board; OD – Optical density; OGC – Oculogyric crises; PD – Pharmacodynamic; PDMS-2 – Peabody Developmental Motor Scale 2nd edition; PET – Positron emission tomography; pHC - Proportion of subjects achieving full head control; pSS - Proportion of subjects able to stand with support; pSU - Proportion of subjects able to sit unassisted; pWA - Proportion of subjects able to walk with assistance; REB – Research ethics board; TEAE – Treatment-emergent adverse events

B.2.3.1 Study data patient population and methodology differences

B.2.3.1.1. Study baseline characteristics

Baseline characteristics were similar across the three studies supporting eladocagene exuparvovec and were broadly representative of patients with severe AADC deficiency in the UK

A summary of the baseline characteristics for the three clinical trials that examine the clinical efficacy and safety of eladocagene exuparvovec is provided in Table 12. Patient baseline characteristics across the three studies were broadly representative of the population likely to receive eladocagene exuparvovec in UK clinical practice:

Age: Mean age at baseline was similar across the three studies, ranging from 52.50–55.00 months (equivalent to 4.38–4.58 years of age). UK clinical experts stated the age of patients when receiving eladocagene exuparvovec in the UK would be similar to those in the clinical studies.[5]

Weight and height: Failure to gain weight is a typical characteristic in patients with AADC deficiency, who experience severe growth retardation relative to normal children.[6] The baseline weight across the trials for eladocagene exuparvovec ranged from 11.17–12.70, which is below the fifth percentile for normal children of similar age. UK clinical experts agreed that the baseline height and weight in trials for eladocagene exuparvovec were representative of patients with severe AADC deficiency in the UK.[5]

Sex: The proportion of male to female patients was similar across all trials for eladocagene exuparvovec (47% females, 53% males). According to natural history studies and consensus guidelines, there is no link between sex and prevalence or phenotype of AADC deficiency.[6,2]

Race: As noted in clinical consensus guidelines, AADC deficiency is most prevalent in Asia and particularly in Taiwan and Japan due to a founder effect.[2] All three studies supporting eladocagene exuparvovec were conducted at a single centre in Taiwan, and all patients treated with eladocagene exuparvovec were of “Asian-Chinese”, “Asian-other” and “Other” race. While UK clinical experts stated that the geography and race of patients in the study is unlikely to reflect patients with AADC deficiency in the UK, UK clinical experts confirmed that race is not a key factor determining AADC deficiency symptoms or disease outcomes. UK experts also confirmed that race is not expected to impact the efficacy and safety of eladocagene exuparvovec because all patients, regardless of race, have a loss of function genetic mutation that has the resultant effect of no AADC enzyme activity.[5]

Genotype: All patients in the trials had the AADC deficiency founder mutation (IVS6+4A>T). UK clinical experts validated that most patients with AADC deficiency in the UK have the founder mutation, and confirmed the published literature that states that there is no correlation between genotype and phenotype in AADC deficiency.[2,5]

Motor function: All patients included in the three studies had very limited motor function at baseline. This is indicated by the very low total scores in the Peabody Developmental Motor Scales, Second Edition (PDMS-2) and Alberta Infant Motor Scale (AIMS) scores. Baseline

median PDMS-2 scores in the clinical studies for eladocagene exuparvovec ranged from 8.75–14.67, which is broadly in line with PDMS-2 scores reported in a natural history study published by Hwu *et al*. (2017)[6] and below the fifth percentile for normal children of the same age. Similarly, the baseline AIMS scores in the clinical studies for eladocagene exuparvovec were within the first percentile for normal children at the same age and indicated no motor function at baseline.[6] UK clinical experts confirmed that patients with AADC deficiency who are expected to receive eladocagene exuparvovec in the UK are those with very limited motor function.[5]

Table 12: Characteristics of participants in the studies across treatment groups (eladocagene exuparvovec-treated population)[16,18,17]

	Category	AADC-010 (N=10)	AADC-011 (N=12)	AADC-CU/1601 (N=8)
Age at baseline (months)	Mean (SD)	52.50 (30.84)	31.3 (15.65)	58.80 (24.84)
	Median (min, max)	34.00 (21.0, 102.0)	23.5 (19.0, 70.0)	54.0(24.0, 99.0)
Age at diagnosis (months)	Mean (SD)	11.40 (7.04)	12.3 (8.08)	15.84 (9.72)
	Median (min, max)	10.50 (1.0, 29.0)	10.00 (1.0, 28.0)	15.00 (3.96, 29.04)
Baseline height, cm	Mean (SD)	98.60 (17.99)	-	96.00 (8.35)
	Median (min, max)	93.00 (79.0, 126.0)	-	97.50 (85.0, 109.0)
Baseline weight, kg	Mean (SD)	12.70 (4.67)	-	11.49 (2.67)
	Median (min, max)	10.50 (7.7, 20.5)	-	10.45 (8.6, 17.0)
Sex	Male	5 (50.0%)	8 (66.7%)	3 (37.5%)
	Female	5 (50.0%)	4 (33.3%)	5 (62.5%)
Race	Asian-Chinese	9 (90.0%)	8 (66.7%)	0 (0.0%)
	Asian-Others	1 (10.0%)	3 (25.0%)	8 (100%)
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	1 (8.3%)	0 (0.0%)
Genotype	Homozygous founder mutation	6 (60.0%)	4 (33.3%)	7 (87.6%)
	Heterozygous founder mutation	4 (40.0%)	8 (66.7%)	1 (12.5%)
PDMS-2 total score at baseline	Mean (SD)	9.50 (3.92)	17.92 (13.59)	8.75 (5.42)
	Median (min, max)	10.0 (4.00, 15.00)	13.00 (7.0, 56.0)	NR (2.00, 16.00)
AIMS total score at baseline	Mean (SD)	1.60 (0.97)	2.92 (1.88)	2.60 (2.07)
	Median (min, max)	1.00 (1.00, 4.00)	2.50 (1.0, 8.0)	NR (0.00, 5.00)

Source: Clinical study report for AADC-CU/1601, AADC-010 and AADC-011.
Abbreviations: AIMS - Alberta Infant Motor Scale; Cm – centimetre; Kg – Kilogram; Max – Maximum; Min – Minimum; NR – Not recorded; PDMS-2 - Peabody Developmental Motor Scale, Second Edition; SD – Standard deviation

B.2.3.1.2. Eligibility criteria

Eligibility criteria were similar across the three clinical studies for eladocagene exuparvovec. Table 9, Table 10, and Table 11 provide details of the eligibility criteria for AADC-010, AADC-

011, and AADC-CU/1601 respectively. Table 101 in Appendix D1.2 provides information on ineligible patients from the pre-screening procedure.

B.2.3.1.3. Patient withdrawal

In all three studies, an individual was discontinued from the study if their legal guardian withdrew consent and all data collected prior to discontinuation or loss to follow-up were to be included in the statistical analyses. Across all three studies, no missing value imputation was used (i.e. all analyses were based on the observed data). It should be noted that two patients in the AADC-011 study, both treated with the higher dose, were not able to attend Month 12 follow-up visits due to the COVID-19 pandemic.

Across the three studies, 2 patients were lost to follow-up and 1 patient was withdrawn per investigator decision. The 2 patients lost to follow-up (both AADC-CU/1601) withdrew due to inability to attend the voluntary Month 60 visit. The 1 withdrawn patient (AADC-010) had influenza B and died of encephalitis due to influenza B after 12.2 months of follow-up. Both the influenza event and death were not related to eladocagene exuparvovec according to investigator assessment. See Table 102 in Appendix D1.2 for information on patient withdrawal across the studies.

B.2.3.1.4. Delivery of intervention

Across the three studies (AADC-010, AADC-011 and AADC-CU/1601), eladocagene exuparvovec was delivered in the same way to all patients, with a total dose of $1.8x10^{11}$ vg infused in 4 sites (2 per putamen) during a single surgical session. AADC-011 also tested a dose of $2.4x10^{11}$ vg, which was delivered via the same method. See Table 103 in Appendix D1.2 for a patient treatment and delivery breakdown.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Across all three studies, statistical analyses were conducted in the ITT population

Across all three studies, the intention-to-treat (ITT) population was used for statistical analyses. AADC-CU/1601 and AADC-010 applied the same statistical approach to conduct analysis on the primary hypothesis. This involved a sequential gatekeeping procedure where an order of hypothesis, relating to each progressive level of milestone, were tested until a failure to reject was encountered. This allowed the level of motor milestone achievement to be determined. Both trials applied this structure at the 60-month endpoint as the primary analysis, using a one-sided test and 0.025 level of significance.

In the AADC-011 study, the number and proportion of patients achieving each key motor milestone was computed at Month 12. Due to limited number of patient data at the time of analysis, no formal statistical hypothesis was tested. Table 13 summarises the statistical analyses in each of the clinical studies supporting eladocagene exuparvovec (AADC-010, AADC-011 and AADC-CU/1601).

Please see Appendix D1.2 for information on participant flow in the relevant studies.

Table 13: Statistical analyses in AADC-010, AADC-011 and AADC-CU/1601 [72,73]

Trial number/ name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawal
AADC-010:	The number and proportion of patients achieving each key motor milestone was computed at 5 years post-gene-replacement therapy. At the 5-year timepoint, the number and proportion of patients achieving each key motor milestone was computed. All efficacy analyses (including statistical analyses) were conducted on the ITT population. The safety population was used for the safety analyses.	The following tests were conducted on the primary efficacy endpoint milestone data at the 60-month timepoint under a sequential gatekeeping procedure, using a 1-sample exact binomial test at a 1-sided α=0.025 level of significance: 1) H0: pHC = p0(HC) vs. H1: pHC >p0(HC) 2) H0: pSU = p0(SU) vs. H1: pSU >p0(SU) 3) H0: pSS = p0(SS) vs. H1: pSS >p0(SS) 4) H0: pWA = p0(WA) vs. H1: pWA >p0(WA) pHC: proportion of subjects achieving full head control pSU: proportion of subjects able to sit unassisted pSS: proportion of subjects able to stand with support pWA: proportion of subjects able to walk with assistance.	N=10. Statistical power = 0.95	1 patient (10%) withdrew between month 12 and month 24 per investigator decision and died after 12.2 months of follow-up. Patients were counted once in this analysis according to their entire duration of follow-up.

		Under the sequential gatekeeping procedure, the hypothesis for head control was tested, and if the null was rejected, then the hypothesis for sitting unassisted was tested. This process continued until 1 of the primary endpoints failed to reject its respective null hypothesis or until the fourth set of hypotheses had been tested.		
AADC-011	The number and proportion of patients achieving each key motor milestone was computed at month 12. All efficacy analyses (including statistical analyses) were conducted on the ITT population. The safety population was used for the safety analyses.	Due to the limited number of patient data at the time of analysis, no formal statistical hypothesis was tested. Medical history of patients enrolled in this study was evaluated for the achievement of these milestones prior to gene-replacement therapy.	N=12.	No patients withdrew or were lost to follow-up.
AADC-CU/1601	The proportion of patients who: 1) achieved full head control 2) were able to sit unassisted 3) were able to stand with support 4) were able to walk with assistance, as measured using the PDMS-2 at 60 months post-gene-replacement therapy. All efficacy analyses (including statistical analyses) were conducted on the ITT population. The safety population was used for the safety analyses.	The following tests were conducted on the primary efficacy endpoint milestone data at the 60-month timepoint under a sequential gatekeeping procedure, using a one-sample exact test at a one-sided α=0.025 level of significance: 1. H0: pHC = p0(HC) vs. H1: pHC >p0(HC) 2. H0: pSU = p0(SU) vs. H1: pSU >p0(SU) 3. H0: pSS = p0(SS) vs. H1: pSS >p0(SS) 4. H0: pWA = p0(WA) vs. H1: pWA >p0(WA), pHC: proportion of subjects achieving full head control pSU: proportion of subjects able to sit unassisted pSS: proportion of subjects able to stand with support pWA: proportion of subjects able to walk with assistance. Under the sequential gatekeeping procedure, the hypotheses for head control were tested first, and if the null was rejected, then the	N=8. Statistical power = 0.95	2 patients (25%) were lost to follow-up between month 24 and month 60 due to the inability to attend the month 60 visit. Withdrawn patients did not need to be followed-up after discontinuation. All data collected prior to discontinuation or loss of follow-up were included in the statistical analyses.

		hypothesis for sitting unassisted was tested. The process continued until one of the primary endpoints failed to reject its respective null hypothesis or until the fourth set of hypotheses had been tested.		

Source: Statistical analysis report for AADC-CU/1601, AADC-010 and AADC-011.
Abbreviations: CIs – Confidence intervals; pHC - Proportion of subjects achieving full head control; pSS - Proportion of subjects able to stand with support; pSU - Proportion of subjects able to sit unassisted; pWA - Proportion of subjects able to walk with assistance; SAP – Statistical analysis plan

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

While the studies supporting eladocagene exuparvovec have limitations inherent to studies for ultra-rare diseases, appropriate measures were taken to ensure their quality Table 105, Table 106Table 107 in Appendix D1.4 provide a critical appraisal of the three clinical studies supporting eladocagene exuparvovec (AADC-010, AADC-011 and AADC-CU/1601). The quality assessment was based on information in the clinical study protocols, reports, and statistical analysis plans.

Studies for eladocagene exuparvovec have limitations inherent to studies for ultra-rare and severe conditions. All studies were single-centre, included low patient numbers, and were single-arm. This is to be expected given that AADC deficiency is ultra-rare with no disease-modifying treatments, meaning it may be considered unethical to include a placebo-control arm. In addition, AADC-CU/1601 was a retrospective observational study. It should be noted that the trials supporting eladocagene exuparvovec included approximately 10% of all patients with AADC deficiency worldwide.

While all three studies face challenges driven largely by the challenges of an ultra-rare and relatively unknown disease and lack of clinical studies, the quality assessment reveals that appropriate measures were taken to manage potential biases. These include prospectively defining inclusion and exclusion criteria, appropriate outcomes, attempting to control for covariates, and transparent reporting of follow-up, outcomes, and statistical analyses.

The studies broadly reflect how eladocagene exuparvovec is expected to be used in UK clinical practice. UK clinical experts validated that, aside from patient ethnicity, the baseline characteristics of patients in the studies aligned with those in the UK.[5] UK experts noted that the ethnicity of the patient would not impact disease outcomes or outcomes with treatment.[5] They also pointed out that the Gross Motor Function Measure-88 (GMFM-88) instrument is normally used to measure motor function in UK practice.[5] While PDMS-2 was used in the trials for eladocagene exuparvovec, PDMS-2 is similar to GMFM-88 and is a well-validated and widely accepted scale globally and provides a comprehensive and complete method for assessing motor milestone achievement. UK clinical experts also noted that improvements in motor milestones correlate well with HRQoL in AADC deficiency patients. [5]

In addition to the quality assessment of the clinical studies, please see Table 104 in Appendix D for a quality assessment checklist for the non-RCT publications identified in the SLR.

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1 AADC-010 efficacy results

The safety and efficacy of eladocagene exuparvovec were evaluated in a Phase I/II single-centre, prospective, single-arm study named AADC-010. The information in this section is sourced primarily from the clinical study report for the AADC-010 trial[18].

B.2.6.1.1. AADC-010: Efficacy summary

- **Motor milestone improvement (primary endpoint):** At baseline, all 10 patients had no motor function. Following treatment with eladocagene exuparvovec, at Month 60 there were significant increases in the proportion of patients achieving head control ([redacted]% of patients), sitting unassisted ([redacted]%), standing with support ([redacted]%), and walking with assistance ([redacted]%).[18]
- **Motor function improvement:** In addition to achieving key motor milestones, motor function was also improved at Month 60 following eladocagene exuparvovec treatment. Patients gained the ability to hold their head while pulling up to sit, sit with support, crawl, and free walk. PDMS-2, AIMS and Bayley-III total scores improved for all treated subjects (100%) over the study, and AIMS and Bayley-III subscale scores increased from baseline. Improved fine motor skills of grasping were also observed following treatment.[18]
- **Body weight:** Mean body weight significantly (p=0.0011) increased over time from baseline to Month 60 in patients treated with eladocagene exuparvovec.[18]
- **Neurological comorbidities:** The incidence of floppiness, limb dystonia, stimulus-provoked dystonia, and OGC facial dyskinesia decreased during the first year following treatment with eladocagene exuparvovec. Notably, the proportion of time spent in OGC episodes was sustainably reduced over time and up to 12 months after treatment.[18]
- **Infections:** The annual rate of respiratory tract infections/pneumonia decreased after treatment with eladocagene exuparvovec, regardless of acquisition of head control. There was a reduced rate of infection from baseline up to 60 months after treatment.[18]
- **Dopamine production:** Eladocagene exuparvovec treatment led to de novo expression of dopamine in the putamen and increased neurotransmitter metabolites in the CSF, indicating that the clinical benefits are due to successful AADC gene transduction.[18]

B.2.6.1.2. Primary efficacy endpoint – motor milestone achievement

Patients with AADC deficiency experience significant improvements in motor milestones following treatment with eladocagene exuparvovec

Patients with severe AADC deficiency typically do not achieve any motor milestones during their lifetime and remain with no motor function.[2,6] At baseline in the AADC-010 study, all patients had no motor function, highlighting the devastating nature of AADC deficiency.

In AADC-010, treatment with eladocagene exuparvovec was associated with rapid, durable, and considerable improvements in motor milestone achievement. By month 60, [redacted]% of patients mastered full head control, [redacted]% mastered sitting unassisted, [redacted]% mastered standing with support, and [redacted]% mastered walking with assistance (Table 14). Mastery was defined as a score of 2 of 2 on the PDMS-2 milestone item.

Table 14: AADC-010 motor milestone achievement (ITT population)[18]

Motor Milestone	Timepoint	Patients, N (%)
No motor function	Baseline (n=10)	10 (100%)
Head control	Baseline (n=10)	[redacted]
	Month 12 (n=10)	[redacted]
	Month 24 (n=9)*	[redacted]
	Month 60 (n=8)*	[redacted]
Sitting unassisted	Baseline (n=10)	[redacted]
	Month 12 (n=10)	[redacted]
	Month 24 (n=9)*	[redacted]
	Month 60 (n=8)*	[redacted]
Standing with support	Baseline (n=10)	[redacted]
	Month 12 (n=10)	[redacted]
	Month 24 (n=9)*	[redacted]
	Month 60 (n=8)*	[redacted]
Walking with assistance	Baseline (n=10)	[redacted]
	Month 12 (n=10)	[redacted]
	Month 24 (n=9)*	[redacted]
	Month 60 (n=8)*	[redacted]

**Patients lost to follow up. See section B.2.3.1 for information on patients lost to follow up.*
Abbreviations: CI – Confidence intervals; ITT – Intent-to-treat
Note: Assessed = PDMS-2 scores of 0,1 or 2; mastery = PDMS-2 scores of 2
Source: Clinical study report for AADC-010 (N=10)

In addition to mastery (PDMS-2 score of 2/2 on the motor milestone item), PDMS-2 scores of 1 out of 2 on the milestone item were defined as emerging skills. As shown in Table 15, the number of patients with partial head control, sitting with support, crawling, and free walking increased over time in patients treated with eladocagene exuparvovec and improvements were sustained. At month 60, [redacted]% of patients achieved emerging or mastery of the most advanced milestone (walking).

Table 15: AADC-010 - Number of subjects achieving key and additional motor milestone acquisition (newly emerging and mastery) within each time interval up to month 60 after eladocagene exuparvovec treatment (ITT population)[18]

	Baseline	Time interval post-treatment (months)						Last assessment post-treatment (up to Month 60)
Motor Milestone[a]	**Baseline (N=10)**	**0–3 (N=10)**	**3–12 (N=10)**	**12– 24 (N=9)**	**24–36 (N=8)**	**36–48 (N=8)**	**48–60 (N=8)**	**Month 60 (N=10)**
Partial head control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Full head control	[redacted]							
Sitting with support	[redacted]							
Sitting unassisted[b]	[redacted]							
Crawling	[redacted]							
Standing with support[b]	[redacted]							
Walking with assistance[b]	[redacted]							
Free walking	[redacted]							

Abbreviations: ITT – Intent-to-treat; PDMS-2 – Peabody developmental motor scale, second edition
Note: Assessed = PDMS-2 scores of 0,1 or 2; emerging and mastery = PDMS-2 scores of 1 or 2
a: Assessed = PDMS-2 scores 0,1 or 2
b: Milestones assessed in the MAA original statistical analysis.
Source: Clinical study report for AADC-010 (N=10)

B.2.6.1.3. Secondary efficacy endpoints – motor development: PDMS-2

Patients with AADC deficiency experience significant increases in PDMS-2 total and subscale scores after treatment with eladocagene exuparvovec

In addition to improvement in key motor milestones, patients treated with eladocagene exuparvovec experience rapid, durable, and significant improvements in motor function, as measured by PDMS-2 scores. From baseline to Month 60, there was a statistically significant improvement in PDMS-2 least squares mean total scores ($p<0.0001$; Figure 15). PDMS-2 subscale scores were also considerably increased from baseline at Month 24 (Figure 16). All 10 eladocagene exuparvovec-treated patients (100%) showed increases in PDMS-2 total scores over time (Figure 17).

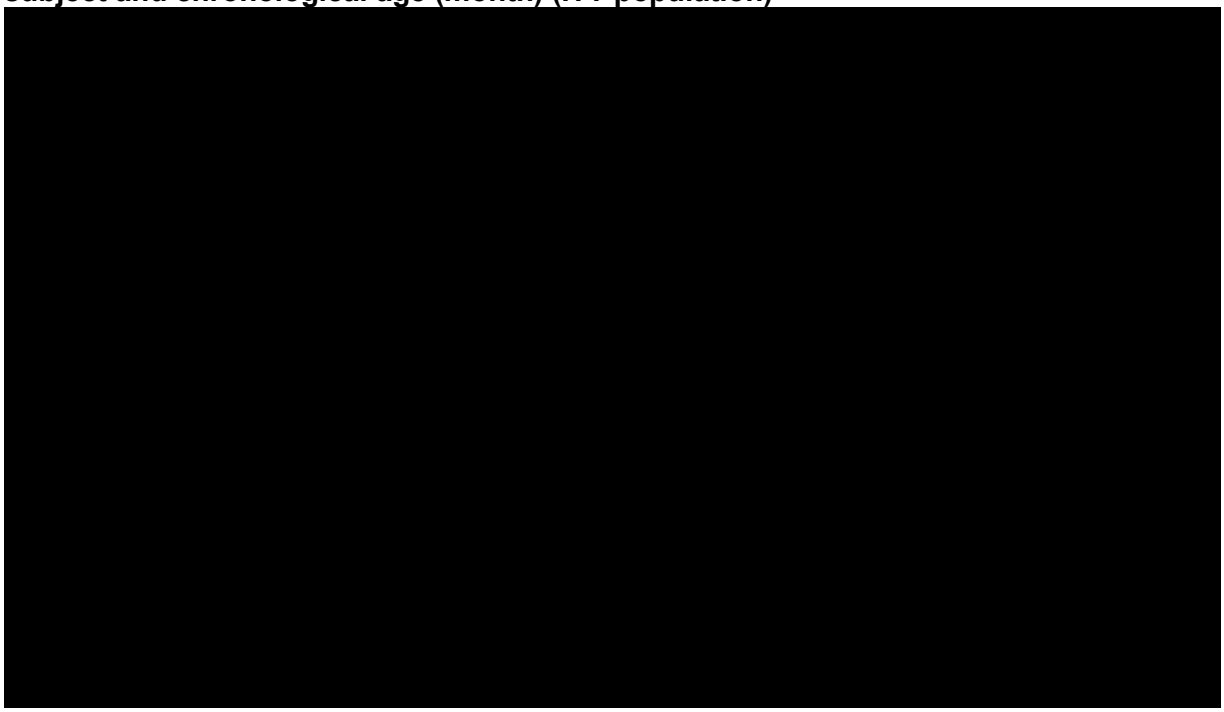
Figure 15: AADC-010 - LS means of change from baseline in AIMS total scores up to 60 months after eladocagene exuparvovec administration (ITT population)[18]

Abbreviations: CFB – Change from baseline; ITT – Intent-to-treat; LS – Least squares; PDMS-2 – Peabody Development Motor Scales-2nd Edition.
Source: Clinical study report for AADC-010 (N=10)

Figure 16: AADC-010 - LS means for PDMS-2 subscales at 2 years after eladocagene exuparvovec administration (ITT population)[18]

Abbreviations: ITT – Intent-to-treat; LCL – Lower confidence limit; PDMS-2 – Peabody Development Motor Scales-2nd Edition; UCL – Upper confidence limit; LS – Least squares
Source: Clinical study report for AADC-010 (N=10)

Figure 17: AADC-010 - PDMS-2 total scores by eladocagene exuparvovec-treated - subject and chronological age (month) (ITT population)[18]



Abbreviations: ITT – Intent-to-treat; PDMS-2 – Peabody developmental motor scales, 2nd edition
Source: Clinical study report for AADC-010 (N=10)

In addition to improving PDMS-2 total and subscale scores, patients also improved on specific skills on those PDMS-2 subscales that represent additional evidence of clinical benefit and development toward more independent motor function, such as sitting, symmetrical posture, rolling, manipulating a rattle and paper, engaging one's own fingers, reaching for a rattle, removing socks, and turning pages.

Taken together, eladocagene exuparvovec considerably improves motor function in patients with AADC deficiency.

B.2.6.1.4. Secondary efficacy endpoints – motor development: AIMS

Patients with AADC deficiency experience significant increases in AIMS total and subscale score following treatment with eladocagene exuparvovec

As with improvements in motor milestones and PDMS-2 scores, patients treated with eladocagene exuparvovec experience rapid, durable, and significant improvement in AIMS score from baseline. Compared with baseline, treatment with eladocagene exuparvovec led to a statistically significant ($p<0.0001$) improvement in AIMS total score at Month 60 (Figure 18). Eladocagene exuparvovec also led to considerably improved AIMS subscale scores at Month 60 (Figure 19). Both total and subscale AIMS score improvements were observed from 3 months onwards.

Figure 18: AADC-010 - LS means of change from baseline in AIMS total scores up to 60 months after eladocagene exuparvovec administration (ITT population)[18]

Abbreviations: AIMS – Albert Infant Motor Scale; ITT – Intent-to-treat; LS – Least squares.
Source: Clinical study report for AADC-010 (N=10)

Figure 19: AADC-010 - LS means for change from baseline for AIMS subscales after eladocagene exuparvovec administration (ITT population)[18]

Abbreviations: AIMS – Albert Infant Motor Scale; ITT – Intent-to-treat; LCL – Lower confidence limit; LS – Least squares; UCL – Upper confidence limit
Source: Clinical study report for AADC-010 (N=10)

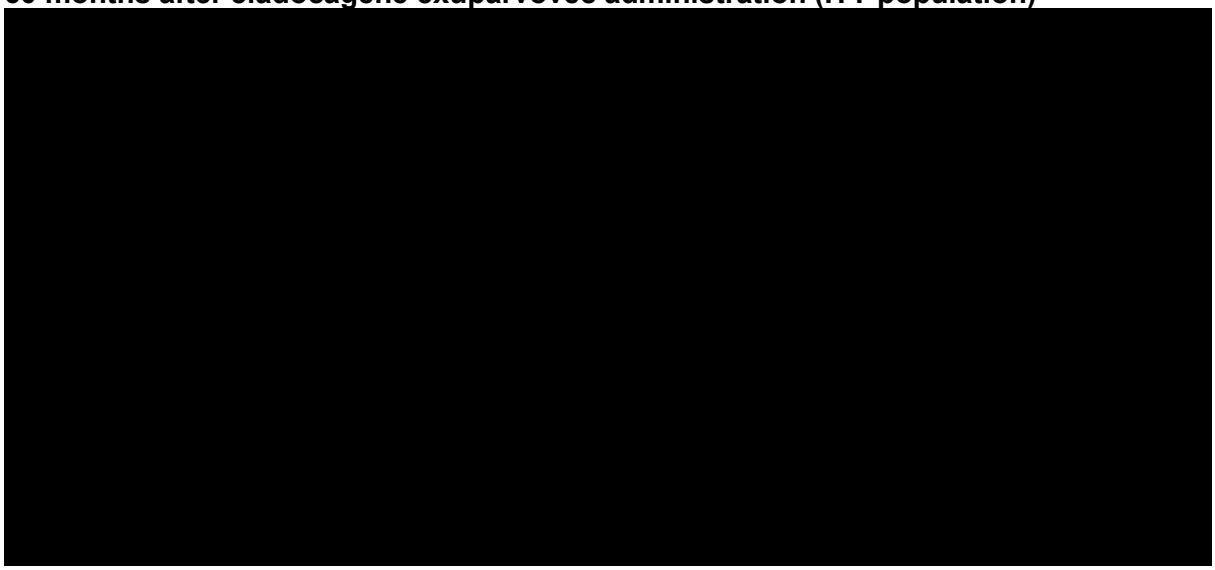
B.2.6.1.5. Secondary efficacy endpoints – cognitive/language development: Bayley-III

Patients with AADC deficiency experience significant increases in Bayley-III total and subscale score following treatment with eladocagene exuparvovec, from as early as 3 months

As described in Section B.2.3.1, patients with severe AADC deficiency experience severe cognitive and language impairment. Bayley-III was therefore included in AADC-010 as a measure of development in infants and toddlers, including cognitive, language, motor, social-emotional, and adaptive functioning.

Patients treated with eladocagene exuparvovec in AADC-010 experience rapid, durable, and significant improvements in development, as measured by Bayley-III. At Month 60, total Bayley-III score was significantly improved versus baseline ($p<0.0001$; Figure 20), with improvement seen as early as Month 3. Patients also considerably improved in Bayley-III subscale scores at Month 60 (Figure 21). Patients also demonstrated specific skills on the Bayley-III that represent additional evidence of clinical benefit and development toward independent motor function, such as grasping a food pellet or toy when not previously able.

Figure 20: AADC-010 - LS mean for change from baseline Bayley-III total scores up to 60 months after eladocagene exuparvovec administration (ITT population)[18]



Abbreviations: Bayley-III – Bayley Scales of Infant Development, Third Edition; ITT – Intent-to-treat; LS – Least squares
Source: Clinical study report for AADC-010 (N=10)

Figure 21: AADC-010 - LS means for change from baseline for Bayley-III subscales at 5 years after eladocagene exuparvovec administration (ITT population)[18]

Abbreviations: Bayley-III – Bayley Scales of Infant Development, Third Edition; ITT – Intent-to-treat; LCL – Lower confidence limit; UCL – Upper confidence limit
Source: Clinical study report for AADC-010 (N=10)

B.2.6.1.6. Secondary efficacy endpoints – body weight

Patients with AADC deficiency experience significant increases in body weight following treatment with eladocagene exuparvovec

As with AADC-CU/1601, treatment with eladocagene exuparvovec in AADC-010 led to a statistically significant increase in mean body weight from baseline to Month 12 (p=0.0011). All but 1 subject maintained weight within the same percentile as baseline or moved to a higher weight percentile after receiving eladocagene exuparvovec.

B.2.6.1.7. Secondary efficacy endpoints – neurologic examination findings

Eladocagene exuparvovec is associated with a reduction in neurologic-related comorbidities from baseline

Following treatment with eladocagene exuparvovec, the number of subjects with floppiness, limb dystonia, stimulus-provoked limb dystonia, and OGC facial dyskinesia decreased at Month 12. In most cases, a reduction in the number of patients with these neurologic findings was apparent as early as Month 3 following treatment. Notably, limb dystonia and stimulus-provoked limb dystonia did not occur in any subject at the Month 6, Month 9, or Month 12.

Eladocagene exuparvovec reduces OGC frequency and duration compared to baseline

OGC is a common and severely debilitating neurological symptom experienced by patients with AADC deficiency (See Section B.1.3.3 for more information). Following treatment with eladocagene exuparvovec, the frequency of OGC episodes and the number of hours per week spent experiencing OGCs decreased steadily from baseline (Table 16). In the 5-week interval before gene-replacement therapy, patients (N=9 with data) experienced OGC activity for a mean period of [redacted] hours/week. Following eladocagene exuparvovec, OGC activity reduced by a mean of [redacted] hours/week at 3 months (N=8), [redacted] hours/week at 6 months (N=8), [redacted] hours/week at 9 months (N=6), and [redacted] hours/week at 12 months (N=6), indicating a pronounced and sustained improvement in OGC. In addition, cases of oculogyric facial dyskinesia decreased over time, occurring in [redacted]% of patients at baseline compared with [redacted]% of patients at Month 12.

Table 16: AADC-010 - Summary statistics for time subjects experienced OGC in hours per week following eladocagene exuparvovec treatment[18]

Interval	Statistics	Observed Values	Change from baseline (Hours/Week)
Baseline	n	[redacted]	-
	Mean (Std)	[redacted]	-
	Median	[redacted]	-
	Min, Max	[redacted]	-
Month 3	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 9	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Abbreviations: Max – Maximum; Min – Minimum
Source: Clinical study report for AADC-010 (N=10)

B.2.6.1.8. Pharmacodynamics – change from baseline in neurotransmitter metabolites

Treatment with eladocagene exuparvovec leads to increased dopamine production

The presence of neurotransmitter metabolites HVA (the metabolite of dopamine) and 5-HIAA (the metabolite of serotonin) was measured in CSF during the first year of follow-up. At Month 12, levels of both HVA and 5-HIAA had increased compared with baseline (Table 17).

Table 17: AADC-010: Neurotransmitter metabolites by timepoint following eladocagene exuparvovec treatment (ITT population)[18]

Metabolite		Baseline (N=10)	CFB at Month 12 (N=9)
HVA	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]
5-HIAA	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]

Abbreviations: 5-HIAA – 5-hydroxyindoleacetic acid; CFB – Change from baseline; HVA – Homovanillic acid; Max – Maximum; Min – Minimum
Source: Clinical study report for AADC-010 (N=10)

B.2.6.1.9. Pharmacodynamic endpoints – F-DOPA PET uptake

Eladocagene exuparvovec increases putaminal dopamine production, as indicated by increased F-DOPA PET uptake

In AADC-010, eladocagene exuparvovec treatment was associated with increased putaminal F-DOPA production, indicating AADC gene transduction and dopamine production. Prior to treatment, no dopamine production was detected. Following infusion of the gene-replacement therapy, an increase from baseline in putaminal-specific uptake of F-DOPA was observed at Month 12, 24, and 60. The increase from baseline was significant at Month 60 ($p<0.0001$), demonstrating a durable increase in AADC gene activity (Table 18).

Table 18: AADC-010 - Putaminal-specific F-DOPA production following eladocagene exuparvovec treatment (ITT population)[18]

	Baseline	Month 12	Month 24	Month 60	P-value
Patients, N	10	9	8	8	-
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	-
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	-
95% CI of LS mean	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001

Abbreviations: CI - Confidence interval; ITT – intention-to-treat; LL - Lower limit; LS - Least squares; N/A - Not applicable; PET - Positron emission tomography; SD - Standard deviation; SE – standard error
Source: Clinical study report for AADC-010 (N=10)

B.2.6.2 AADC-011 efficacy results

AADC-011 is a single-arm, single-centre, Phase I/II study exploring the efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency (see Section B.2.3 for study design information).[17]

The AADC-011 study explored a dose of 1.8×10^{11} vg, given to patients 3 years and older (n=3), and a dose of 2.4×10^{11} vg, given to patients less than 3 years old (n=9). Given that the EMA concluded that efficacy and safety in the two doses were similar both doses are reported in this submission to utilise the full data available given the limited sample size.

This section reports baseline characteristics and primary and secondary efficacy endpoints for all subjects. The information in this section is sourced primarily from the clinical study report for the AADC-011 trial[17].

AADC-011 recorded only 12-months of efficacy data, in comparison to the 60-month lengths of AADC-010 and AADC-CU/1601. It should also be noted that two patients in the AADC-011 study were not able to attend Month 12 follow-up visits due to the COVID-19 pandemic. Consequently, some efficacy improvement may not yet be realised in this study. However, patient improvements in efficacy observed at the 12-month timepoint are comparable between AADC-010, AADC-011, and AADC-CU/1601, suggesting further improvement can be expected in later years after treatment for the cohort in AADC-011.[17]

B.2.6.2.1. AADC-011 - Efficacy summary

- **Motor milestones:** Motor development improved within 12-months, with [redacted] patients achieving head control and [redacted] of patients achieving sitting unassisted at Month 12, compared with 0% at baseline. Further improvements in emerging and mastery of skills were observed across most patients in partial head control (achieved by [redacted]% of patients) and sitting with assistance (achieved by [redacted]% of patients).[17]
- **Motor function:** Rapid improvement in motor development was observed, with PDMS-2 and AIMS total and subscale scores increasing significantly to 12 months.
- **Cognition and language skills:** Improved from baseline, demonstrated by Bayley-III total, and subscale scores significantly increasing.
- **Body weight:** Body weight increased with mean change from baseline of [redacted] kg.
- **Neurological comorbidities:** Floppiness, OGC, oculogyric facial dyskinesia, limb dystonia and myoclonus, sufferer numbers decreased as early as 3 months and continued for 1 year after treatment.
- **AADC enzyme activity:** HVA metabolite increases in the CSF and putaminal-specific PET uptake of F-DOPA indicate that eladocagene exuparvovec leads to dopamine production.
- **Muscle power and fine motor grasping:** Scores improved within 1 year of treatment. The mean fine motor grasping total score was 0.17 at baseline and increased to [redacted] at Month 12.

B.2.6.2.2. Primary efficacy endpoint – motor milestone achievement

Patients with AADC deficiency experienced improvements in motor milestones following treatment with eladocagene exuparvovec

In line with the AADC-CU/1601 and AADC-010 studies, achievement of key motor milestones at Month 12 was the primary endpoint for AADC-011. All patients had no motor function at baseline. Not all subjects were able to return for follow-up visits, primarily due to the COVID-

19 pandemic; as such, only 9 of the 12 enrolled subjects were assessed for the primary endpoint. At Month 12, [redacted] of the 9 subjects ([redacted]%) had achieved head control, and [redacted] subjects ([redacted]%) were able to sit unassisted (Table 19).

Patient improvement in milestone achievement is comparable to that observed in AADC-CU/1601 and AADC-010 for the same timepoint, suggesting further improvement can be expected in later years after treatment.

Table 19: AADC-011 - Number and proportion of eladocagene exuparvovec-treated subjects achieving key motor milestones at Month 12[17]

Motor Milestone	Patients, N (%)*
Head Control	[redacted]
Sitting Unassisted	[redacted]
Standing with Support	[redacted]
Walking with Assistance	[redacted]

Abbreviations: PDMS-2 - Peabody Developmental Motor Scales-Second Edition; vg - Vector genome
**9 of 12 enrolled subjects were able to attend the Month 12 visit, partly due to COVID-19*
Source: Clinical study report for AADC-011 – Table 14.2.1.1.3 (N=12)

Figure 22: AADC-011 - Cumulative proportion of subjects who achieved emerging and mastery of motor milestones by time point following eladocagene exuparvovec treatment[17]

[redacted]

Source: Clinical study report for AADC-011 (N=12)

As displayed in Table 20, additional motor milestones were also assessed for mastery alongside the 4 key motor milestones. Improvements from baseline can be observed in partial head control, head control, sitting with assistance and sitting unassisted, some as early as 3 months. Not all subjects were assessed at all timepoints; hence, the number of subjects assessed at each timepoint is shown as the denominator for each timepoint.

Table 20: AADC-011 - Key and additional motor milestones (emerging and mastery) by time point following eladocagene exuparvovec treatment

Milestone (Emerging and Mastery)	Number of Subjects Assessed by Timepoint, n/N* (%)				
	Baseline	Month 3	Month 6	Month 9	Month 12
Partial head control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Head control	0/12	[redacted]	[redacted]	[redacted]	[redacted]
Sitting with assistance	0/12	[redacted]	[redacted]	[redacted]	[redacted]
Sitting unassisted	0/12	[redacted]	[redacted]	[redacted]	[redacted]
Crawling	0/12	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support	0/12	[redacted]	[redacted]	[redacted]	[redacted]
Walking with assistance	0/12	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PDMS-2 - Peabody developmental motor scale, second edition
**The number of subjects assessed at each timepoint is shown.*
Source: Clinical study report for AADC-011 – Table 14.2.1.4.3 (N=12)

B.2.6.2.3. Secondary efficacy endpoints – motor development: PDMS-2

Patients with AADC deficiency experience significant increases in PDMS-2 total and subscale scores following treatment with eladocagene exuparvovec

Figure 23 displays the PDMS-2 total score LS means for the 12-month length of AADC-011. Improvements in scores for patients can be observed with a statistically significant change from the baseline to the 12-month endpoint ($p<0.0001$). Figure 24 displays the PDMS-2 subscale scores LS means for the 12-month length of AADC-011, where substantial increases can also be observed and score improvements can be observed for the 12-month study length. All 12 eladocagene exuparvovec-treated patients (100%) showed increases in PDMS-2 total scores over time.

Figure 23: AADC-011 - LS Means for change from baseline in PDMS-2 total scores by time point following eladocagene exuparvovec treatment[17]

Abbreviations: CFB - Change from baseline; LS - Least squares; PDMS-2 - Peabody developmental motor scale, second edition
Source: Clinical study report for AADC-011 (N=12)

Figure 24: AADC-011 - Forest plot of LS means for change from baseline in PDMS-2 subscale scores at month 12 after eladocagene exuparvovec treatment[17]

Abbreviations: LCL - Lower control limit; LS - Least squares; PDMS-2 - Peabody Developmental Motor Score, second edition; UCL - Upper control limit
Source: Clinical study report for AADC-011 (N=12)

Increases in mean values for the grasping, locomotion, stationary, and visual-motor integration PDMS-2 subscales were observed from baseline to Month 12. All subjects demonstrated

improvement of specific skills on the PDMS-2 subscales that represent additional evidence of clinical benefit and development toward more independent motor function, including sitting, rolling, manipulating a rattle and paper, and removing pegs. From an individual patient perspective, all subjects showed increases in PDMS-2 total scores over time (Figure 25).

Figure 25: AADC-011 - PDMS-2 total scores by subject and chronological age in months following eladocagene exuparvovec treatment[17]

Abbreviations: PDMS-2 – Peabody developmental motor scale, second edition
Source: Clinical study report for AADC-011 – Figure 14.2.2.6.1 (N=12)

B.2.6.2.4. Secondary efficacy endpoints – motor development: AIMS

Patients with AADC deficiency experience significant increases in AIMS total and subscale score following treatment with eladocagene exuparvovec

Figure 26 displays the AIMS total score LS means for the 12-month duration of the AADC-011 study. A statistically significant ($p<0.0001$) change can be observed between the baseline and 12-month timepoint. Figure 27, which covers the subscale AIMS scores LS means also demonstrates the considerable increase. Both total and subscale AIMS score improvements can be observed from 3 months and throughout the study.

Figure 26: AADC-011 - LS means for change from baseline in AIMS total scores by time point following eladocagene exuparvovec treatment[17]

Abbreviations: AIMS-Alberta infant motor scale; CFB-Change from baseline; LS-Least squares
Source: Clinical study report for AADC-011 (N=12)

Figure 27: AADC-011 - Forest plot of LS means for change from baseline in AIMS subscale scores at month 12 after eladocagene exuparvovec treatment[17]

Abbreviations: AIMS-Alberta infant motor scale; LCL-Lower confidence limit; LS-Least squares; UCL-upper confidence limit
Source: Clinical study report for AADC-011 (N=12)

B.2.6.2.5. Secondary endpoint – cognitive/language development: Bayley-III

Patients with AADC deficiency experience significant increases in Bayley-III total and subscale score from as early as 3 months after treatment with eladocagene exuparvovec,

Figure 28 displays the Bayley-III total score LS means for the 12-month duration of the AADC-011 study. A statistically significant ($p<0.0001$) change can be observed between the baseline and 12-month timepoint. This demonstrates improvement in cognitive and language skills. Improvements in Bayley-III total scores for most subjects can be observed as early as 3 months after treatment. Figure 29, which covers the Bayley-III subscale scores, also indicates considerable improvement throughout the study period. In the subscale monitoring, the largest improvements were observed in the cognitive domain.

Figure 28: AADC-011 - LS mean for change from baseline in Bayley-III total scores by time point following eladocagene exuparvovec treatment[17]

Abbreviations: Bayley-III - Bayley scales of infant and toddler development, third edition; CFB - Change from baseline; LS - Least squares
Source: Clinical study report for AADC-011 (N=12)

Figure 29: AADC-011 - Forest plot of LS means for change form baseline in Bayley-III subscales at month 12 following eladocagene exuparvovec treatment[17]

Abbreviations: Bayley-III - Bayley Scales of Infant and Toddler Development, third edition; LCL - Lower control limit; LS - Least squares; UCL - Upper control limit
Source: Clinical study report for AADC-011 (N=12)

B.2.6.2.6. Secondary efficacy endpoints – body weight

Patients with AADC deficiency experience increases in body weight over the study length, following treatment with either dose of eladocagene exuparvovec

As discussed in Section B.2.3.1, lack of body weight is a recognised symptom of AADC deficiency. Mean body weight increased from baseline to Month 12. For all subjects, mean change from baseline in body weight was [redacted] kg at Month 12 (p=0.0015) (Table 21).

Table 21: AADC-011 Mean body weight among patients treated

Time point	Body weight in kg, mean (SD)	Change from baseline in kg, mean (SD)	P-value
Baseline	9.62 (1.34)	-	
3-month	[redacted]	[redacted]	
6-month	[redacted]	[redacted]	
9-month	[redacted]	[redacted]	
12-month	[redacted]	[redacted]	0.0015

Abbreviations: SD – standard deviation
Source: Clinical study report for AADC-011 - Table 14.2.5.1.3 (N=12)

B.2.6.2.7. Secondary efficacy endpoints – neurologic examination findings

Neurological examination findings demonstrate decreases in the proportion of patients suffering with various comorbidities, following treatment with eladocagene exuparvovec

Following eladocagene exuparvovec gene-replacement therapy, the number of subjects with dysphagia, floppiness, OGC, and limb dystonia decreased by Month 12. In most cases, reductions in the number of subjects with these neurologic findings were apparent as early as Month 3 following treatment. Cases of generalized choreoathetosis, oculogyric facial dyskinesia, stimulus-provoked dystonia, distal chorea, flexor spasm, and myoclonus remained similar or unchanged after treatment.

Further analyses of OGC episodes revealed that the number of hours per week spent experiencing OGC fluctuated over time but generally decreased in the 3 months following treatment with eladocagene exuparvovec (Table 22).

Table 22: AADC-011 - Summary statistics for time eladocagene exuparvovec-treated subjects experienced oculogyric crisis in hours per week

Interval	Statistics	Observed Values (Hours/Week)	Change from Baseline (Hours/Week)
Baseline	n	12	-
	Mean (Std)	10.30 (1.820)	-
	Median	10.07	-
	Min, Max	7.81, 14.25	-
Month 1	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 2	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 3	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Abbreviations: max - Maximum; min - Minimum; OGC - Oculogyric crises; std - Standard deviation
Note: Baseline is the average of data within 5 weeks before gene-replacement therapy. The time points after gene-replacement therapy include data from 2 weeks prior to the selected timepoint, the week of that timepoint, and the 2 weeks after the selected timepoint.
Source: Clinical study report for AADC-011 – Table 14.2.6.3.3 (N=12)

B.2.6.2.8. Pharmacodynamics: change from baseline in neurotransmitter metabolites

Dopamine metabolites increased in patients following treatment with eladocagene exuparvovec

The presence of neurotransmitter metabolites HVA (the metabolite of dopamine) and 5-HIAA (the metabolite of serotonin) were measured in CSF during the first 12 months of follow-up. At Month 12, the concentration of HVA increased compared with baseline. The presence of 5 HIAA in CSF decreased slightly compared with baseline (Table 23).

Table 23: AADC-011 - Neurotransmitter metabolites by timepoint following eladocagene exuparvovec treatment

	Baseline N=10	CFB at Month 12 N=8
HVA (nmol/L)		
Mean (SD)	17.80 (16.65)	[redacted]
Median (min, max)	11.00 (2.50, 47.00)	[redacted]
5-HIAA (nmol/L)		
Mean (SD)	7.85 (7.78)	[redacted]
Median (min, max)	3.75 (2.50, 21.00)	[redacted]

Abbreviations: 5-HIAA – 5-Hydroxyindoleacetic acid; CFB – Change from baseline; HVA - Homovanillic acid; Max - Maximum; Min - Minimum; SD - Standard deviation
Source: Clinical study report for AADC-011 – Table 14.2.10.1.3 (N=12)

B.2.6.2.9. Pharmacodynamics: F-DOPA uptake

Putaminal-specific F-DOPA increased in patients following treatment with eladocagene exuparvovec

Expression and activity of the AADC enzyme in the putamen was assessed by PET imaging using F-DOPA, a positron-emitting fluorine-labelled version of levodopa, a substrate for AADC. Prior to treatment (baseline evaluation), minimal dopamine production was detected using PET. On average, an increase from baseline in putaminal-specific uptake of F-DOPA was observed at 12 months after receiving gene-replacement therapy (Table 24).

Table 24: AADC-011 - Summary statistics for putaminal PET-specific uptake by time point following eladocagene exuparvovec treatment

	Baseline (N=10)	CFB at Month 12 (N=9)	P-value
Mean (SD)	0.32 (0.17)	[redacted]	N/A
Median (min, max)	0.35 (0.09, 0.55)	[redacted]	N/A
95% CI of Mean (UCL, LCL)	0.22, 0.43	[redacted]	0.0345

Abbreviations: LCL – Lower confidence limit; Max - Maximum; Min - Minimum; PET - Positron emission tomography; SD - Standard deviation; UCL – Upper confidence limit
Source: Clinical study report for AADC-011 – Table 14.2.11.1.3 (N=12)

B.2.6.3 AADC-CU/1601 efficacy results

The information stated in this section is sourced primarily from the clinical study report for the AADC-CU/1601 trial[16]. This was the initial compassionate use programme and clinical study that, combined, aimed to retroactively evaluate the safety and efficacy of eladocagene exuparvovec in children with AADC deficiency for a period of up to 60 months after study drug administration.

The ITT Population was used for efficacy endpoint analyses. This population consisted of all enrolled patients (N=8). Because all patients received eladocagene exuparvovec treatment, the ITT population was the same as the Safety Population.

B.2.6.3.1. AADC-CU/1601: Efficacy summary

- **Motor milestone improvement:** At baseline, all patients had no motor function. Following treatment with eladocagene exuparvovec, [redacted] patients ([redacted]%) treated with eladocagene exuparvovec achieved full head control at months 12, 24 and 60. [redacted] patients could sit unassisted at 12 months, whilst [redacted] patients achieved this milestone at the 24- and 60-month timepoints. Standing with support was achieved by [redacted] patients at the 60-month timepoint.[16]
- **Durability of effect:** Continued motor development was observed beyond 60 months, with [redacted] gaining the ability to walk with assistance. Though the sequential testing hypothesis structure led to this not being analysed, an improvement was observed compared to pre-treatment.[16]
- **Global outcome improvements:** General increases in PDMS-2, AIMS and CDIIT total and subscale scores were observed throughout the trial following treatment. Statistically significant increases were observed for Least Squares (LS) Mean AIMS total scores and CDIIT whole test scores. Improvement was observed very early and continued throughout the trial length, demonstrating improved acquisition and maintenance of skills following treatment with eladocagene exuparvovec.[16]
- **Movement disorders:** The number of patients with floppiness, OGC episodes, limb dystonia, and stimulus-provoked dystonia decreased during the first year after eladocagene exuparvovec infusion. No patients required new treatment with a dopaminergic agent, which is a widely used treatment as part of BSC in patients with no motor function.[16]
- **No immunogenicity:** No correlation was observed between anti-AAV2 antibody titre and efficacy as measured by changes in PDMS-2 total score.[16]
- **F-DOPA PET uptake:** Increases in mean putaminal-specific uptake of dopamine on PET imaging was evident as early as Month 6 and further increased through Month 60, indicating the presence of functional AADC enzyme. This allowed for restoration of dopamine in deep brain structures and contributes to improvement in motor function.[16]

B.2.6.3.2. Primary efficacy endpoint – motor milestone achievement

Patients with AADC deficiency experience significant improvements in motor milestones following treatment with eladocagene exuparvovec

Treatment with eladocagene exuparvovec resulted in clinical benefits in terms of motor milestone achievement in all eight AADC deficiency patients in the AADC-CU/1601 study. At baseline, all 8 patients had no motor function. At month 60, [redacted]% of patients mastered head control and sitting unassisted, whilst [redacted]% of patients were able to stand with support (Table 25). Over time, the proportion of patients achieving each motor milestone increased, indicating that the benefits of eladocagene exuparvovec are sustained and patients continue to improve up to at least Month 60 following treatment.

Table 25: AADC-CU/1601 - Number and proportion of patients treated with eladocagene exuparvovec achieving key motor milestone (ITT population[16])

Motor milestone	Timepoint	Patients, N (proportion)	95% CI for proportion
Head control	Baseline	0 (0.0)	(0.0, 0.4)
	12 months	[redacted]	[redacted]
	24 months	[redacted]	[redacted]
	60 months	[redacted]	[redacted]
Sitting unassisted	Baseline	0 (0.0)	(0.0, 0.4)
	12 months	[redacted]	[redacted]
	24 months	[redacted]	[redacted]
	60 months	[redacted]	[redacted]
Standing with support	Baseline	0 (0.0)	(0.0, 0.4)
	12 months	[redacted]	[redacted]
	24 months	[redacted]	[redacted]
	60 months	[redacted]	[redacted]
Walking with assistance	Baseline	0 (0.0)	(0.0, 0.4)
	12 months	[redacted]	[redacted]
	24 months	[redacted]	[redacted]
	60 months	[redacted]	[redacted]

Source: Clinical study report for AADC-CU/1601 (N=8)
Abbreviations: CI – Confidence intervals; ITT – Intent-to-treat; N/A – Not applicable

B.2.6.3.3. Secondary efficacy endpoints – motor development: PDMS-2

Patients with AADC deficiency experience significant increases in PDMS-2 total and subscale scores following treatment with eladocagene exuparvovec, from as early as 3 months

In addition to improved motor milestones, patients treated with eladocagene exuparvovec experience progressive and sustained improvements in PDMS-2 scores, indicating improved motor function following treatment. Improvements in total PDMS-2 scores for patients can be observed from 3 months and continue throughout, with a statistically significant change from the baseline at the Month 60 endpoint ($p<0.0001$; Figure 30). When assessed by visit using

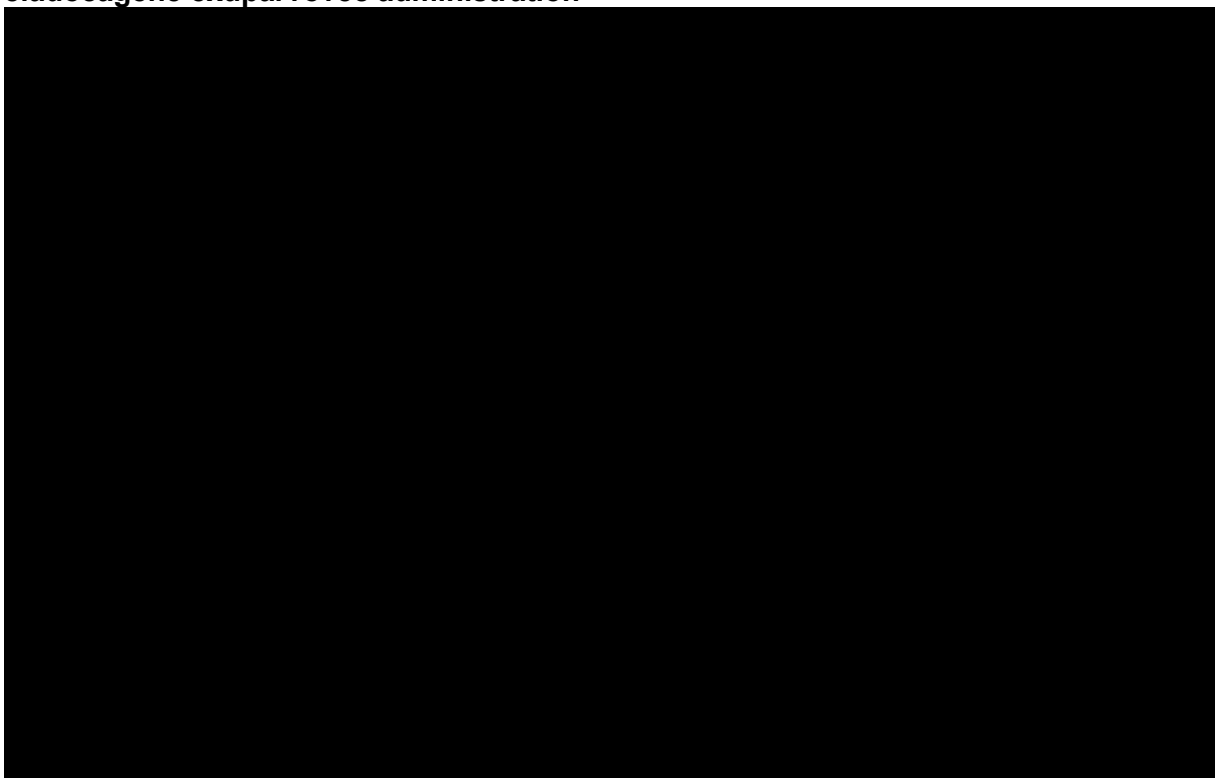
repeated measures mixed effects models, treatment with eladocagene exuparvovec led to consistently statistically significant improved PDMS-2 scores (p≤0.003).

In addition to improved total PDMS-2 scores, eladocagene exuparvovec was associated with improved PDMS-2 subscale scores from as early as Month 3 and observed at month 60 (Figure 31). Patients also demonstrated improvement of specific skills on the PDMS-2 subscales that represent additional evidence of clinical benefit and development toward more independent motor function, including sitting, rolling, grasping a rattle or cube, removing pegs, and placing cubes.

Figure 30: AADC-CU/1601 - LS means of PDMS-2 total scores up to 60 months after eladocagene exuparvovec administration (ITT population)[16]

PDMS-2 total baseline mean: 8.75. Note: p<0.0001 for LS mean for CFB at month 60 using a repeated measures model with terms for timepoint, age at gene-replacement therapy and baseline score. Two-sided p-value was used for testing null hypothesis): LS mean = 0 for the total CFB score at month 60. CFB = (score at the current time point) – (baseline score).
Abbreviations: CFB – Change from baseline; ITT – Intent-to-treat; LS – Least squares; PDMS – Peabody developmental motor scales, second edition
Source: Clinical study report for AADC-CU/1601 (N=8)

Figure 31: AADC-CU/1601 - LS means for PDMS-2 subscale scores 60 months after eladocagene exuparvovec administration[16]



PDMS-2 subscale baseline mean scores: Visual motor integration: 2.38, Stationary: 3.00, Object manipulation: 0.00, Locomotion: 0.63, Grasping: 2.75. Improvement in reflexes was not significant and is not shown due to data for only N=3 patients.
Abbreviations: ITT – Intent-to-treat; LCL – Lower control limit; LS – Least squares; PDMS – Peabody developmental motor scales, second edition; UCL – Upper control limit
Source: Clinical study report for AADC-CU/1601 (N=8)

B.2.6.3.4. Secondary efficacy endpoints – motor development: AIMS

Patients with AADC deficiency experience significant increases in AIMS total and subscale score following treatment with eladocagene exuparvovec

Further evidence of the benefit of eladocagene exuparvovec on patient motor function is demonstrated through the considerable improvement in AIMS total score at Month 60. A statistically significant ($p<0.0001$) and durable improvement from baseline following eladocagene exuparvovec was observed at the 60-month timepoint, with improvements observed from as early as month 3 (Figure 32). Increases of 30 or more points were observed in 3 patients, indicating marked improvements in motor function from the mean baseline score of 2.60. In addition to substantially improved AIMS total score, eladocagene exuparvovec treatment leads to considerable improvements in AIMS subscale scores (Figure 33).

Figure 32: AADC-CU/1601 - LS means of AIMS total scores up to 60 months after eladocagene exuparvovec administration (ITT population)[16]

AIMS total baseline mean: 2.60. AIMS score ranges from 0–58, with higher score indicating better motor function. Note: p<0.0001 for LS mean for CFB at month 60 using a repeated measures model with terms for timepoint, age at gene-replacement therapy and baseline score. Two-sided p-value was used for testing H): LS mean = 0 for the total CFB score at month 60. CFB = (score at the current time point) – (baseline score).
Abbreviations: AIMS – Albert infant motor scale; CFB – Change from baseline; ITT – Intent-to-treat; LS – Least squares. Source: Clinical study report for AADC-CU/1601 (N=8)

Figure 33: AADC-CU/1601 - LS means for AIMS subscale scores 60 months after eladocagene exuparvovec administration (ITT population)[16]

AIMS subscale baseline mean: Supine: 1.00, Stand: 0.60, Sit: 0.40, Prone: 0.60. Higher AIMS score denotes better motor function. Abbreviations: AIMS – Albert infant motor scale; ITT – Intent-to-treat; LCL – Lower control limit; LS – Least squares; UCL – Upper control limit. Source: Clinical study report for AADC-CU/1601 (N=8)

B.2.6.3.5. Secondary efficacy endpoints – Comprehensive Developmental Inventory for Infants and Toddlers test (CDIIT)

Patients with AADC deficiency experience significant increases in CDIIT total and subscale score following treatment with eladocagene exuparvovec

In addition to improving motor function, AADC-CU/1601 data indicate that treatment with eladocagene exuparvovec is associated with rapid, durable, and statistically significant improvements in development (including cognition, language, motor skills, and self-care skills), as indicated by CDIIT scores. Compared with baseline, a statistically significant ($p<0.0001$) improvement in CDIIT scores was observed at Month 60, with improvements observed from as early as Month 6 (Figure 34). As with PDMS-2 and AIMS, there were also considerable improvements in CDIIT subscale scores at Month 60 versus baseline (Figure 35).

Figure 34: AADC-CU/1601 - LS means of CDIIT total scores up to 60 months after eladocagene exuparvovec administration (ITT population)[16]

CDIIT baseline mean score: 21.75. Higher CDIIT score indicates improvement. Total possible score is dependent on the age of the patient.
Note: p<0.0001 for LS mean for CFB at month 60 using a repeated measures model with terms for timepoint, age at gene-replacement therapy and baseline score. Two-sided p-value was used for testing H0: LS mean = 0 for the total CFB score at month 60. CFB = (score at the current time point) – (baseline score).
Abbreviations: CDIIT – Comprehensive developmental inventory for infants and toddlers; CFB – Change from baseline; ITT – Intent-to-treat; LS – Least squares.
Source: Clinical study report for AADC-CU/1601 (N=8)

Figure 35: AADC-CU/1601 - LS means for CDIIT subscale scores 60 months after Eladocagene Exuparvovec administration (ITT population)[16]

CDIIT subscale baseline scores: social: 11.13, self-help: 1.50, motor total score: 0.13, language: 5.75, Cognition: 3.25, fine motor: 0.13, gross motor: 0.00
Abbreviations: CDIIT – Comprehensive developmental inventory for infants and toddlers; ITT – Intent-to-treat; LCL – Lower control limit; LS – Least squares; UCL – Upper control limit.
Source: Clinical study report for AADC-CU/1601 (N=8)

B.2.6.3.6. Secondary efficacy endpoints – body weight

Patients with AADC deficiency experience significant increases in body weight following treatment with eladocagene exuparvovec

As discussed in Section B.2.3.1, lack of body weight is a recognised symptom of AADC deficiency. Treatment with eladocagene exuparvovec leads to rapid, sustained, and significant increase in body weight from baseline to Month 60 (Figure 36). A clear and statistically significant increase can be observed from baseline to Month 60 (p=0.0270).

Figure 36: AADC-CU/1601 - Mean bodyweight (Kg) over time following eladocagene exuparvovec (ITT population)[16]

Baseline body weight mean: 11.49kg.
Abbreviations: CFB – Change from baseline; ITT – Intent-to-treat
Source: Clinical study report for AADC-CU/1601 (N=8)
Note: p=0.0270 for mean CFB at month 60. Two-sided p-value from one-sample t-test of H0: CFB=0 at month 60. CFB = (weight at the current time point) – (baseline weight).

B.2.6.3.7. Secondary efficacy endpoints – neurologic examination findings

The proportion of patients suffering various neurological-related comorbidities decreases following treatment with eladocagene exuparvovec

Treatment with eladocagene exuparvovec also led to a reduction in neurological-related comorbidities compared with baseline. Most of the patients had neurologic findings on examination at baseline, and the number of patients with floppiness, OGC episodes, limb dystonia, and stimulus-provoked- dystonia appeared to decrease during the first year following treatment with eladocagene exuparvovec.

Figure 67, Figure 68, Figure 69 and Figure 70 in Appendix M: Additional clinical information, provide a graphical representations of OGC episodes, limb dystonia, and stimulus-provoked dystonia during the 12-month period after eladocagene exuparvovec administration.

B.2.6.3.8. Pharmacodynamics – change from baseline in neurotransmitter metabolites

Neurotransmitter metabolite data indicate an increase in dopamine production following treatment with eladocagene exuparvovec

The presence of the neurotransmitter metabolites, homovanillic acid (HVA; the metabolite of dopamine) and 5-hydroxyindoleacetic acid (5-HIAA; the metabolite of serotonin), were measured in CSF during the first year of follow-up. The concentration of HVA at Month 6 and Month 12 was increased following treatment with eladocagene exuparvovec compared with baseline, indicating dopamine production. The concentration of 5-HIAA was slightly increased at Month 6, with no change from baseline at Month 12.

B.2.6.3.9. Pharmacodynamics – F-DOPA PET scan results

Putaminal-specific F-DOPA PET uptake data indicate a functioning AADC gene following treatment with eladocagene exuparvovec

Putaminal-specific F-DOPA PET was measured as a marker of AADC gene transduction and de novo dopamine production. Following treatment with eladocagene exuparvovec, putaminal-specific F-DOPA PET uptake was evident as early as Month 6 and further increased through Month 60 (Figure 37). F-DOPA PET uptake increased over time, as supported by an observed increase in LS mean putaminal-specific uptake from Month 6 and through to Month 12 and Month 60. The magnitude of change in putaminal-specific uptake was not associated with age (p=0.2516).

See Table 139, Table 140 and Figure 71 in Appendix M for summary statistics of putaminal-specific F-DOPA PET uptake.

Figure 37: AADC-CU/1601 - Least squares means and standard errors for putaminal-specific uptake by timepoint following eladocagene exuparvovec treatment (ITT population)[16]

Baseline putaminal-specific uptake mean: 0.13
Abbreviations: ITT – Intent-to-treat
Source: Clinical study report for AADC-CU/1601 (N=8)

B.2.7. Subgroup analysis

No subgroup analyses were performed in any of the three individual studies for eladocagene exuparvovec.

B.2.8. Meta-analysis

As described in Section B.2.1.1, there are no head-to-head clinical studies comparing eladocagene exuparvovec to BSC. AADC deficiency is an ultra-rare and very severe disease with no licensed disease-modifying treatments. All three clinical trials for eladocagene exuparvovec are single arm due to the low patient numbers and because a control arm is challenging for ethical reasons. As such, it is not possible to conduct a standard pair-wise meta-analysis for the studies supporting eladocagene exuparvovec.

B.2.9. Indirect and mixed treatment comparisons

As only single arm clinical trial data exists for eladocagene exuparvovec, an indirect treatment comparison (ITC) has been explored to evaluate the feasibility of conducting analyses to generate sufficiently robust estimates for the comparative effectiveness of eladocagene exuparvovec compared to BSC. Unfortunately, conducting a sufficiently robust adjusted ITC

using the patient-level data available for eladocagene exuparvovec and BSC is not feasible. The data and methodologies explored are discussed in further detail below.

B.2.9.1 Study identification

B.2.9.1.1. Identification of studies for the ITC feasibility assessment

As described in Section B.2.1, an SLR was performed to identify all relevant clinical effectiveness evidence related to eladocagene exuparvovec (intervention) and BSC (comparator) in AADC deficiency.

B.2.9.1.2. Eladocagene exuparvovec studies

As described in Section B.2.6, there are three clinical trials (AADC-010[018], AADC-011[17] and AADC-CU/1601[16]) evaluating the clinical effectiveness of eladocagene exuparvovec. All clinical trials were open-label, single-arm and non-RCTs, which is common with ultra-rare conditions where there are no other licenced treatments available.

Due to low patient numbers, all patients (N=28) across the three trials were considered in the ITC feasibility analyses.

B.2.9.1.3. BSC studies

Due to the extremely rare nature of AADC deficiency and lack of licenced treatments options for treating the condition, there are limited data on the natural history of patients. Given the lack of published data on the natural history of patients, a natural history database (NHDB) was compiled by PTC to support regulatory and HTA submissions for eladocagene exuparvovec, predominantly from published case studies.[8] The NHDB was created through a separate, previous SLR that compiled information from all published reports on known AADC deficiency patients (please see Appendix D1.1.8 Summary of trials used for indirect or mixed treatment comparisons for more information**).**[8] The NHDB collected data on patients' sex, age at diagnosis, gene mutations, PDMS-2 and AIMS scores at baseline, disease severity, motor milestone achievement, mortality, and treatment, where available.

The NHDB initially identified 237 likely unique patients, of which 185 were unique patients with strong supporting data to be included in the final version of the NHDB.[8] A total of 163 unique non-PTC subjects were identified. Of patients with sufficient longitudinal data on their disease severity, 49 could be classified as having a similar phenotype to the trial population (AADC deficiency with no or poor head control at 24 months) and were considered for the ITC feasibility assessment.[8] The motor milestone of each patient was estimated through an assessment of the evidence reported in each publication related to quantitative motor function (using tools such as PDMS-2 and AIMS) and qualitative descriptions of individual patient development by the authors. The 49 severe AADC deficiency patients are used in the following analyses.

B.2.9.2 Use of studies in the ITC feasibility analysis

The SLR conducted as part of this NICE appraisal (described in Section B.2.1) identified a further fifteen publications that reported the natural history of the disease and/or disease symptoms/progression (Table 26). None of these studies contained sufficient information to justify their use as a comparator arm within the ITC feasibility assessment, with the rationale for exclusion provided in Table 26.

Table 26: Studies not included in ITC feasibility analyses

Comparator	Study	Rationale for exclusion from ITC
hAADC administered in SNc and VTA	Gupta *et al.*, 2020[74]	BSC arm has insufficient evidence to identify unique patients from data given and thus is not suitable for use in the NHDB.
	Bankiewicz *et al.,* 2019[75]	BSC arm has insufficient evidence to identify unique patients from data given and thus is not suitable for use in the NHDB.
	Pearson *et al.,* 2019[75]	BSC arm has insufficient evidence to identify unique patients from data given and thus is not suitable for use in the NHDB.
	Pearson *et al.,* 2021[76]	BSC arm consists of only data at baseline and is not suitable for use in the NHDB.
	Bankiewicz *et al.,* 2018[77]	BSC arm has suitable data available and is already included in NHDB.
ATMPs	Boehnke *et al.* 2021[78]	Insufficient data (only qualitative assessment) of motor milestone achievement reported.
BSC/ Natural history	Chan *et al.*, 2012[79]	Suitable data available, already included in NHDB.
	Pearson *et al.*, 2020[7]	Indirect information provided (clinician questionnaires), inferior to case reports utilised in NHDB.
	Saberian *et al.*, 2021[80]	Questionnaire data, inferior to case reports utilised in NHDB.
	Williams *et al.*, 2021[51]	Questionnaire data, inferior to case reports utilised in NHDB.
	Wen *et al.*, 2020[44]	Insufficient follow-up/long-term data for use in NHDB.
	Mastrangelo *et al.*, 2019[81]	Not suitable for NHDB as insufficient evidence to identify unique patients from data given.
	Saberian S *et al.* 2021[82]	Indirect information provided (clinician questionnaires), inferior to case reports utilised in NHDB.
	Havalı C *et al.* 2021[83]	No information on motor milestone achievement reported.
	Ling T-K *et al.* 2021[84]	No information on motor milestone achievement reported.
	Boehnke A. *et al*[78]	Insufficient information (only qualitative assessment) of motor milestone achievement reported.

Abbreviations: ATMPs – advanced therapy medicinal products; BSC – Best supportive care; ITC – Indirect treatment comparison; NHDB – Natural History Database

B.2.9.3 ITC methodology selection

ITC methodologies based on individual patient-level data make use of observational or non-randomised individual patient data (IPD).[22] This is applicable to eladocagene exuparvovec, as there are IPD available on the treated population (three single-arm trials, N=28) as well as the

comparator population (NHDB, N=49 characterised with a similar “severe” phenotype as those in the eladocagene exuparvovec studies [i.e., no or poor head control by the age of two]).

As per NICE DSU TSD 17 on the use of observational data to inform estimates of treatment effectiveness for comparative IPD,[22] there are multiple methodologies for an estimate of the treatment effect based on IPD, including multivariate regression, regression adjustment, matching, inverse probability weighting, propensity score matching and regression on propensity score. All these methods rely on a good overlap in the covariate distribution of the treatment and comparator groups, meaning that for any combination of observable characteristics, there is always a chance of finding individuals in both the treatment and comparator groups.[22]

Table 27 shows that there are some differences between patients in the eladocagene exuparvovec and BSC arms, mainly driven by missing data on patients on BSC as collected in the NHDB. In the NHDB, the sex of the patient is not known in 12.2% of patients, the race not known in 20.4% and the mutation category not known in 26.5% of the patients. As such, there is poor overlap between the populations.

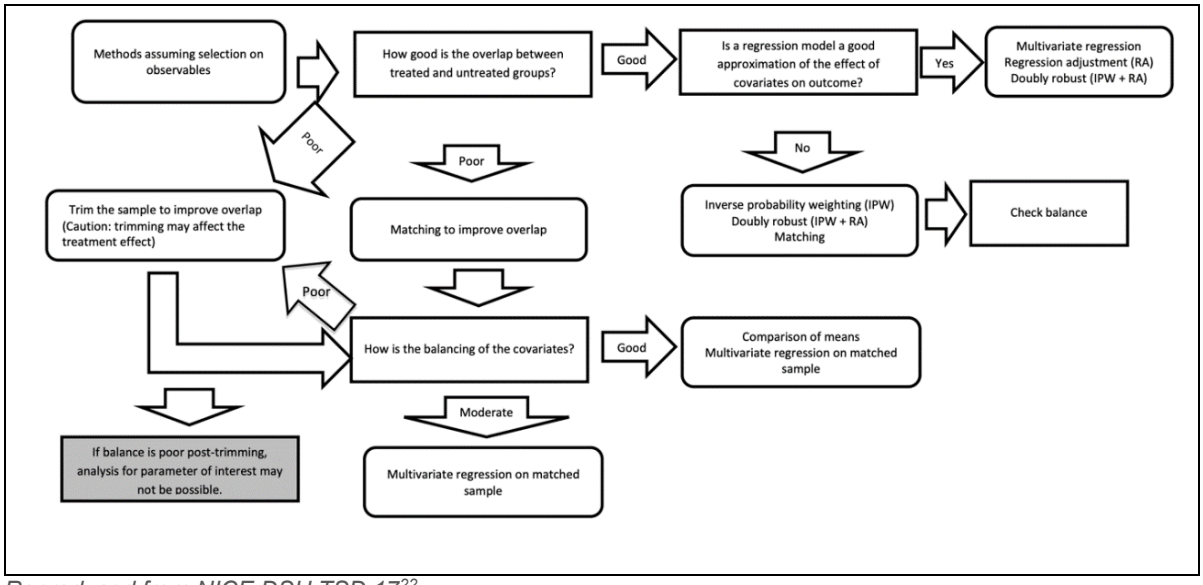
Table 27: Patient characteristics across the natural history database and the three eladocagene exuparvovec trials

	Natural history database[45,858]	Eladocagene exuparvovec[16–18]
N	49	28
Sex		
Female	17 (34.6%)	14 (50.0%)
Male	26 (53.1%)	14 (50.0%)
Unknown	6 (12.2%)	0 (0.0%)
Age at diagnosis, mean (SD)	3.4 (3.5)	3.4 (3.6%)
Race		
Chinese	22 (44.9%)	16 (57.1%)
Japanese	8 (16.3%)	0 (0.0%)
Other Asian	1 (2.0%)	10 (35.7%)
White	8 (16.3%)	1 (3.6%)
Unknown	10 (20.4%)	1 (3.6%)
Mutation category		
Heterogenous	20 (40.8%)	11 (39.3%)
Homogenous	16 (32.7%)	17 (60.7%)
Unknown	13 (26.5%)	0 (0.0%)

Abbreviations: SD – standard deviation

Based on the NICE DSU TSD 17[22] model selection guide shown in Figure 38, propensity score matching was chosen as the primary ITC methodology. This approach was confirmed as appropriate by an external UK statistician with experience developing NICE DSU TSDs for ITCs. Regardless, the level of missingness in the data is a large obstacle to matching the two populations. In propensity score matching analyses, patients are essentially discarded from the analysis if there not a good match in terms of covariates, leading to substantial lost information when there is sparsity in data for covariates being matched.

Figure 38: Proposed algorithm for selection of methods: Methods assuming selection on observables.



Reproduced from NICE DSU TSD 17[22]

B.2.9.4 Matching methodology

An approximate matching exercise was carried out using propensity score matching methods to assess the feasibility of sample sizes when controlling for variables of interest. Further detail is given in Appendix D1.1.8 Summary of trials used for indirect or mixed treatment comparisons).

B.2.9.4.1. Covariate selection

To carry out the matching, a set of variables on which to match upon or control for need to be decided. The set of covariates that are available for both the NHDB and the eladocagene exuparvovec trials is outlined in Table 27. In choosing the set of variables to match upon, there is a bias-variance trade-off, as the more variables that are included in the matching specification, the more information will be lost from the NHDB. Therefore, the aim is to match on the fewest number of variables possible while also trying to reduce the amount of bias.

The covariates considered in the analysis were sex, race, mutation category and age at diagnosis, based on discussions with clinicians.[5,24] Initially, patient age, motor milestone achieved and non-motor symptoms were considered as additional key factors for inclusion as adjustment covariates, but the data on non-motor symptoms were not available from the NHDB. Additionally, the age of the patient and their motor milestone attainment has already been taken into consideration when defining the severe phenotype sample of patients in the NHDB from the whole population (the N=49 patients had not attained a motor milestone by the age of two). In using all the available covariates and the recommendations of clinicians consulted, three model specifications were considered:

a) Sex, race, mutation category and age at diagnosis

b) Sex and race only

c) Sex

B.2.9.4.2. Outcome selection

The proportion of patients who achieved key motor milestones from year 1 to year 5 was assessed. In the eladocagene exuparvovec trials, motor milestones were defined as follows:

- Full head control: The patient was considered successful on this task only if able to sit supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds.
- Sitting unassisted: A patient was considered successful in sitting unassisted only if able to sit without support and maintain balance while in a sitting position for 60 seconds.
- Standing with support: A patient was considered successful at stepping while standing with support only if he/she was able to take at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk, consistent with, standing with support.
- Walking with assistance: A patient was considered successful only if he/she was able to walk at least 8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.

For each patient in the NHDB, the motor development or milestone displayed at either the current visit or since the last visit was extracted from relevant publications where possible.

Motor milestone data for eladocagene exuparvovec (from the three clinical trials) and BSC (from the NHDB) were also analysed in a naïve comparison using a descriptive analysis to compare outcomes in the two arms.

B.2.9.5 Results

Table 28 presents the results of the propensity score matching exercise in terms of the resulting effective sample size of the NHDB. In all analyses, the effective sample size reduces substantially, with less than 5 patients available for analysis when matching by (a) sex, race, mutation category, and age at diagnosis, or (b) sex and race.

Figure 39 presents histograms for the distribution of patient weights after each matching exercise. The distribution of these weights is large in all cases when matching on (a) all variables and (b) sex and race. The effective sample size and the distribution of patient weights for these model specifications indicate that there is a significant loss of information when matching, essentially rendering any results from these analyses meaningless.

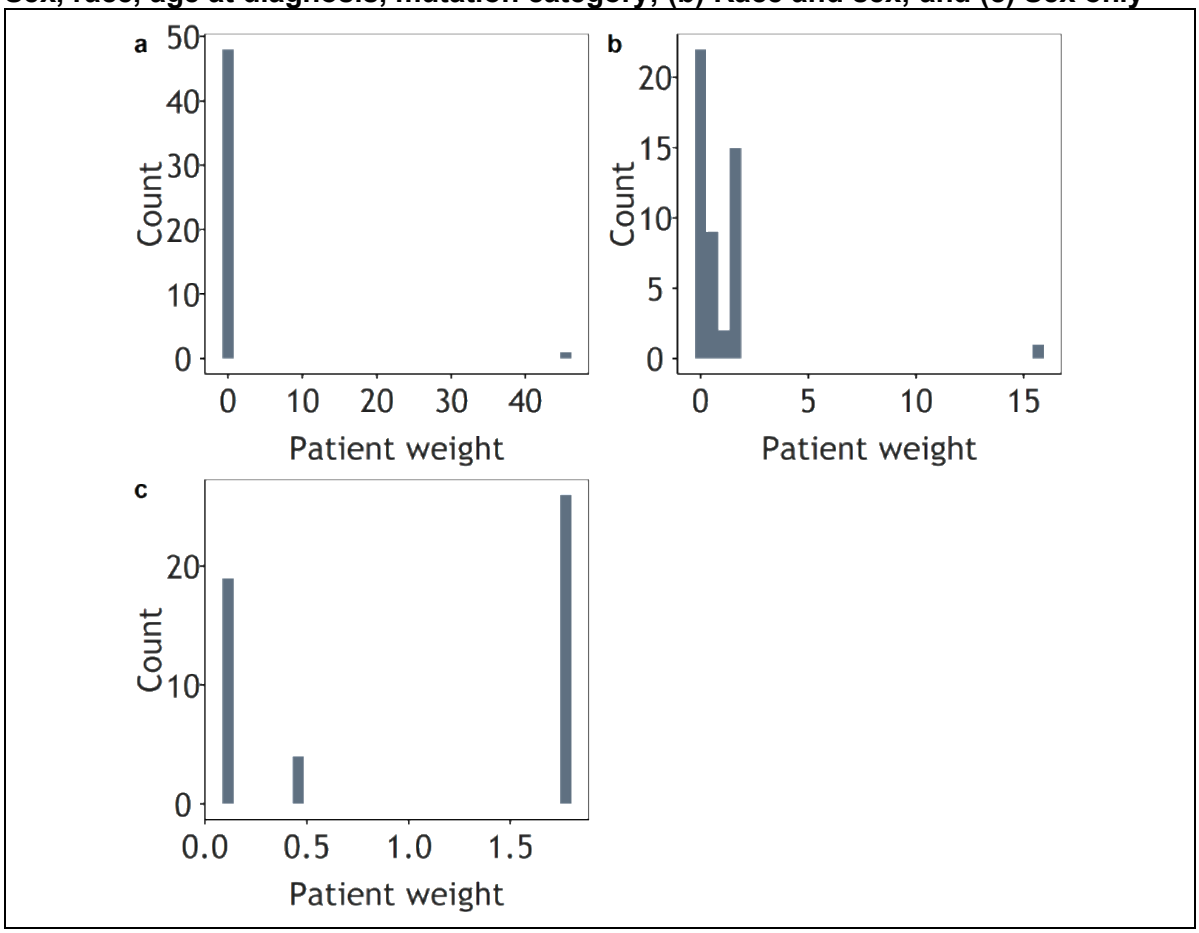
Though effective sample sizes are slightly increased when matching on (c) sex only, this model specification should be rejected because of the distribution of the weights.

Table 28: Effective sample size results from the matching exercise

Matching variables	Effective sample size of NHDB
None	49
(a) Sex, race, mutation category, age at diagnosis	1.16
(b) Sex and race	8.08
(c) Sex	29.81

The very low effective sample size when attempting to match shows that an ITC is not possible.

Figure 39: Distribution of patient weights after the matching analysis for Models (a) Sex, race, age at diagnosis, mutation category; (b) Race and sex; and (c) Sex only



B.2.9.6 Naïve analysis

An analysis on motor milestone achievement trajectory on patients with a severe AADC deficiency phenotype in the NHDB shows that only two out of 49 experience any motor development over a five-year follow-up period. One patient was able to walk with assistance and another was able to roll from side to side.

The naïve analysis of the NHDB suggests that severe AADC deficiency patients receiving BSC show minimal or no improvement in terms of their motor milestone achievement, with 96% of patients achieving no motor milestones over five years (Table 29). A similar analysis

of patients in the three eladocagene exuparvovec trials shows substantial improvements in patients' motor milestones over a similar time period (Table 30). The difference in effectiveness confirms the superiority of eladocagene exuparvovec versus BSC.

Table 29: Distribution of patients across motor milestone health states in the BSC arm

	No motor milestone	Full head alignment	Sitting	Stepping	Walking with assistance
Baseline	100%	0%	0%	0%	0%
Year 1	98%	0%	2%	0%	0%
Year 2	96%	2%	0%	0%	2%
Year 3	96%	0%	2%	0%	2%
Year 4	96%	0%	2%	0%	2%
Year 5 +	96%	0%	2%	0%	2%

The highest motor milestone achieved at that timepoint is reported.

Table 30: Observed distribution of patients across motor milestone health states in the eladocagene exuparvovec arm

	No motor milestone	Full head alignment	Sitting	Stepping	Walking with assistance
Baseline	100%	0%	0%	0%	0%
Year 1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

The highest motor milestone achieved at that timepoint is reported. N=28

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

Due to the ultra-rare nature of AADC deficiency, there is limited information available on the natural history of the disease and in terms of the sample size of patients in clinical trials. The NHDB created by PTC on patients with AADC deficiency, found 49 patients with information indicating a phenotype similar to the patients in the eladocagene exuparvovec studies.

Propensity score matching was found to be the most suitable indirect treatment comparison methodology due to poor overlap between the study covariates. However, any matching carried out on the data vastly reduces the sample size of the population and creates weights that vary widely between patients, indicating unstable matching.[16] Further, the effective sample sizes in the matching on all variables and on sex and were sufficiently low to be infeasible to use. Matching on sex alone was not feasible due to the distribution of the weights. In addition, the lack of heterogeneity between BSC options utilised across individual patients in clinical practice limited the feasibility of conducting an adjusted ITC. Based on this, an ITC was not feasible. The approach to the ITC and the conclusions derived from the feasibility analyses were validated by a UK statistician with experience in the NICE appraisal process and developing NICE TSDs on ITCs.

Based on the factors above, a naïve comparison alone was utilised as the comparative efficacy data for eladocagene exuparvovec and BSC. Naïve analyses have previously been

accepted by NICE, for example in the case of atidarsagene autotemcel for treating metachromatic leukodystrophy (HST18), where an ITC is not feasible.[86] Despite being a naïve comparison, some form of matching has been carried out to ensure that the disease severity is comparable between the comparator and intervention arms by ensuring that the phenotype of the NHDB population was comparable to those individuals receiving eladocagene exuparvovec. The naïve comparison (with some matching to the severity in the trial population) identifies very little development in motor milestone achievement for BSC (96% of BSC patients do not achieve any motor milestones (i.e. do not reach “full head control”), which is in significant contrast to patients treated with eladocagene exuparvovec, who demonstrate substantial improvement in motor milestones at each year following treatment. The disparity in effectiveness demonstrates the superiority of eladocagene exuparvovec versus BSC.

B.2.10. Adverse reactions

Safety data from the three key clinical trials (AADC-010, AADC-011 and AADC-CU/1601) have been pooled into one set of safety data representing the 28 patients treated with eladocagene exuparvovec at a dose of $1.8x10^{11}$ vg or $2.4x10^{11}$ vg. As the EMA concluded that the two doses are similar in terms of efficacy and safety, safety data for both doses have been included in this appraisal.[14]

B.2.10.1 Pooled safety data summary

Eladocagene exuparvovec is associated with mostly mild AEs and a low rate of treatment-related AEs

- **Most of the common AEs were typical symptoms of AADC deficiency:** Of the [redacted] AEs across the 28 patients in the three studies, common AEs included pyrexia, dyskinesia, upper respiratory infection, gastroenteritis, pneumonia, and upper gastrointestinal haemorrhage. At least 1 AE was reported by all patients.
- **AEs were mostly mild or moderate:** Of the [redacted] AEs, [redacted] were mild, [redacted] were moderate, and [redacted] were severe.
- **The majority of AEs were not treatment-related:** Only [redacted] of the [redacted] AEs were considered possibly related to treatment or higher. [redacted] AEs were considered definitely related to treatment.
- **No treatment-related patient deaths:** At the time of analysis of the pooled N=28 data set, [redacted] patients had died following treatment with eladocagene exuparvovec, but none were treatment-related.

B.2.10.2 Exposure

A total of 28 patients received eladocagene exuparvovec across three single-arm studies. The median duration of follow-up in the pooled safety analysis set (N=28) was [redacted] months (min [redacted] months, max [redacted] months).

B.2.10.3 Summary of AEs

Eladocagene exuparvovec is associated with a low rate of treatment-related adverse events

Across all three clinical studies (AADC-010, AADC-011 and AADC-CU/1601), eladocagene exuparvovec was associated with [redacted] AEs and [redacted] serious AEs (SAEs; Table 31). The total number of AEs considered to be possibly, likely, or definitely treatment-related was relatively low ([redacted]) (Table 31).

Table 31: Adverse reactions to eladocagene exuparvovec summary (all studies)

	Patients, N (%)
Total number of TEAEs	[redacted]
Patients with ≥1 TEAEs	[redacted]
Total number of SAEs	[redacted]
Patients with ≥1 SAEs	[redacted]
Total number of AEs possibly/likely related to treatment	[redacted]
Total number of AEs definitely related to treatment	[redacted]
Deaths	[redacted]

**Death confirmed to be non-treatment related*
Abbreviations: SAEs – Serious adverse events; TEAEs – Treatment-emergent adverse events
Source: Integrated Summary of Safety (Table 2.2, Table 2.10) (N=28)

B.2.10.4 Frequency of AEs

Most of the commonly occurring AEs following eladocagene exuparvovec were typical symptoms of AADC deficiency

The most common TEAE, occurring in over 50% of patients treated with eladocagene exuparvovec across the three trials were pyrexia ([redacted]%), dyskinesia ([redacted]%), upper respiratory infection ([redacted]%), gastroenteritis ([redacted]%), pneumonia ([redacted]%), and upper gastrointestinal haemorrhage ([redacted]%; Table 32). These AEs are common features of AADC deficiency. The most common TEAEs occurring up to Month 12 following gene-replacement therapy were pyrexia ([redacted]%), dyskinesia ([redacted]%), upper respiratory tract infection ([redacted]%), pneumonia ([redacted]%), and gastroenteritis ([redacted]%).

Table 32: AEs occurring in ≥2 patients treated with eladocagene exuparvovec

MedDRA Preferred Term	Patients, N (%)
Pyrexia	[redacted]
Dyskinesia	[redacted]
Upper respiratory tract infection	[redacted]
Gastroenteritis	[redacted]
Pneumonia	[redacted]
Upper gastrointestinal haemorrhage	[redacted]
Diarrhoea	[redacted]
Breath sounds abnormal	[redacted]
Anaemia	[redacted]
Gingivitis	[redacted]
Cyanosis	[redacted]
Developmental hip dysplasia	[redacted]
Hypotension	[redacted]
Mouth ulceration	[redacted]
Dehydration	[redacted]
Hypokalaemia	[redacted]
Scoliosis	[redacted]
Dermatitis diaper	[redacted]
Eczema	[redacted]
Tooth extraction	[redacted]
Initial insomnia	[redacted]
Hypovolaemic shock	[redacted]
Dental caries	[redacted]
Gastrooesophageal reflux disease	[redacted]

Bronchitis		[redacted]	
Acute sinusitis			
Bronchiolitis			
Rash			
Nasopharyngitis			
Otitis media acute			
Cerebrospinal fluid leakage			
Feeding disorder			
Irritability			
Choking			
Respiratory failure			
Decubitus ulcer			
Bradycardia			
Laryngomalacia			
Constipation			
Enterocolitis			
Haematochezia			
Oesophageal achalasia			
Salivary hypersecretion			
Stress ulcer			
Hypothermia			
Influenza			
Pneumonia influenzal			
Post procedural pneumonia			
Septic shock			
Urinary tract infection			
Thermal burn			
Hypoglycaemia			
Dystonia			
Apnoea			
Asthma			
Cough			
Hypoxia			
Pneumonia aspiration			
Rhinitis allergic			
Sleep apnoea syndrome			
Shock			

Abbreviations: MedDRA – Medical dictionary for regulatory activities version 24.0; TEAE – Treatment-emergent adverse event
Note: Subjects who had a given TEAE start date on or after date of gene-replacement therapy are counted once.
Source: Integrated Summary of Safety – Table 2.4 (N=28)

B.2.10.5 AEs by severity

B.2.10.5.1. Overall

AEs associated with eladocagene exuparvovec were mostly mild or moderate.

For the 28 patients treated with eladocagene exuparvovec across AADC-010, AADC-011 and AADC-CU/1601, most AEs were mild ([redacted]%), with few severe AEs ([redacted]%) and a small proportion of moderate AEs ([redacted]%; Table 33).

Table 33: TEAE severity (all studies)

Severity	Patients, N (%)
Mild	[redacted]

Moderate	[redacted]
Severe	[redacted]

Abbreviations: TEAEs – Treatment-emergent adverse events
Source: Integrated Summary of Safety – Table 2.12 (N=28)

B.2.10.5.2. Moderate-to-severe TEAEs by preferred term

Among moderate-to-severe TEAEs occurring in the first 12 months following gene-replacement therapy, four occurred in [redacted]% or more patients (Table 34).

Table 34: Moderate-to-severe TEAEs occurring in ≥20% patients at 12 months following gene-replacement therapy (all studies)

	Patients, N (%)	
TEAE by MedDRA Preferred Term	**Moderate**	**Severe**
Pneumonia	[redacted]	[redacted]
Dyskinesia	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]

Abbreviations: MedDRA – Medical dictionary for regulatory activities version 24.0; TEAE – Treatment-emergent adverse event; TEAE – Treatment-emergent adverse events
Source: Integrated Summary of Safety – Table 2.11 (N=28)

B.2.10.6 Treatment-related TEAEs

Most AEs across the three clinical studies were unrelated to eladocagene exuparvovec

While there was a high number of AEs throughout the trial, most were considered unrelated to treatment with eladocagene exuparvovec. In an analysis of the 28 patients treated with eladocagene exuparvovec, most patients had a TEAE with "possible" or "probable" relationship to treatment, but [redacted] patients had a TEAE with "certain" relationship to treatment.

- Across the three studies, of the [redacted] AEs, [redacted] were possibly related or higher (Table 35). No patients experienced AEs which were categorised as certainly related to eladocagene exuparvovec (Table 36).
- The most frequent treatment-related AE was dyskinesia, as expected given the de novo production of dopamine following eladocagene exuparvovec gene-replacement therapy, and consistent with AE reports from clinical experience (AADC-CU/1601). Other AEs considered possibly related to treatment included initial insomnia, sleep disorder, salivary hypersecretion and feeding difficulty.

Table 35: Treatment-related AEs following eladocagene exuparvovec treatment

Adverse event category	Pooled (%)
Total number of AEs considered possibly related or higher	[redacted]
Patients with ≥1 treatment related AE	[redacted]
Dyskinesia	[redacted]
Initial insomnia	[redacted]
Sleep disorder	[redacted]
Salivary hypersecretion	[redacted]
Feeding disorder	[redacted]

Abbreviations: AE – Adverse event.
Source: Integrated Summary of Safety – Table 2.24 (N=28)

Table 36: Treatment-related AEs following eladocagene exuparvovec treatment (all studies)

Highest TEAEs relation to treatment	Patients, N (%)
Unrelated	[redacted]
Unlikely/remote	[redacted]
Possible	[redacted]
Probable	[redacted]
Certain	[redacted]

Abbreviations: TEAEs – Treatment-emergent adverse events
Source: Integrated Summary of Safety – Table 2.2 (N=28)

B.2.10.7 Deaths

No deaths related to eladocagene exuparvovec were recorded during the study period across all three trials.

At the time of the pooled safety analysis (N=28):

- [redacted] treatment-related deaths were reported. [redacted] not related to treatment occurred.
- [redacted] was due to influenza B encephalitis after 12 months of follow-up, considered unrelated to treatment (AADC-010).[87]
- [redacted] was due to complications of AADC deficiency outside the 60-month study period, unlikely to be related to treatment (AADC-CU/1601).[87]

B.2.10.8 Serious adverse events

Across the three studies, a total of [redacted] SAEs were experienced. SAEs occurring in two or more patients are provided in Table 37.

Table 37: Serious adverse events occurring in ≥2 patients following eladocagene exuparvovec treatment

MedDRA Preferred Term	Patients, N (%)
Pneumonia	[redacted]
Gastroenteritis	[redacted]
Upper respiratory tract infection	[redacted]
Dehydration	[redacted]
Hypovolaemic shock	[redacted]
Cyanosis	[redacted]
Upper gastrointestinal haemorrhage	[redacted]
Pyrexia	[redacted]
Bronchiolitis	[redacted]
Post procedural pneumonia	[redacted]
Septic shock	[redacted]
Pneumonia aspiration	[redacted]

Respiratory failure		[redacted]	
Sleep apnoea syndrome		[redacted]	

Abbreviations: MedDRA – Medical dictionary for regulatory activities version 24.0
Note: Subjects who had a given TEAE start date on or after date of gene-replacement therapy are counted once.
Source: Integrated Summary of Safety – Table 2.10 (N=28)

B.2.11. Ongoing studies

There are no ongoing studies. The final CSR for AADC-011 is currently being updated with additional analyses as part of the EMA appraisal process. The EMA regulatory review is expected to conclude in [redacted]. Aside from the final CSR for AADC-011, no further data are expected for studies AADC-010, AADC-011, or AADC-CU/1601.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings

Eladocagene exuparvovec is consistently associated with rapid, significant, and durable improvements in key outcomes related to AADC deficiency

Across three clinical studies (AADC-010, AADC-011, AADC-CU-1601), eladocagene exuparvovec is associated with rapid, significant, and durable improvements from baseline in key outcomes related to AADC deficiency, including motor milestone achievement, motor function, development, cognition, and OGC episodes. Due to the ultra-rare and severe nature of AADC deficiency, all clinical trials were open-label, single-arm, non-RCTs.

The transformative and life-changing benefits of eladocagene exuparvovec are best demonstrated in the videos seen in Tai *et al*., 2022[68] and in the video provided by PTC as part of the EMA Scientific Advisory Group meeting.[19]

B.2.12.2 Efficacy evidence

Across three clinical studies and up to 60 months of follow-up in 28 patients, eladocagene exuparvovec is associated with consistent, rapid, significant, and durable improvements in symptoms related to AADC deficiency. Benefits versus baseline include rapid and/or significant and/or durable improvements in:

- Key motor milestones
- Motor function (PDMS-2, AIMS and CDIIT total and subscale scores)
- Development, language, and cognition (Bayley-III total and subscale scores)
- Body weight
- Neurologic-related comorbidities including OGC frequency and duration

The improvements in AADC deficiency symptoms are likely to be driven by successful and durable AADC gene transduction, as indicated by increased dopamine CSF metabolites and increased putaminal-specific F-DOPA PET uptake.

B.2.12.3 Safety evidence

Across three clinical studies and up to 60 months of follow-up in 28 patients, eladocagene exuparvovec was associated with:

- Mostly mild AEs.
- A low rate of treatment-related Aes.
- [redacted] treatment-related deaths and a relatively low total number of deaths ([redacted] at the time of the pooled safety analysis).
- Most AEs were common symptoms associated with AADC deficiency.

- The most common AEs were dyskinesia, pyrexia, upper respiratory infection, diarrhoea, pneumonia, gastroenteritis, dehydration, abnormal breath sounds, upper gastrointestinal haemorrhage, cyanosis, all of which are typical symptoms of AADC deficiency.

B.2.12.4 Strengths and limitations of the clinical evidence base of technology

The clinical development programme for eladocagene exuparvovec comprises three key clinical trials (AADC-010, AADC-011, AADC-CU-1601), which are phase I, II/IIb and compassionate use trials. All three trials have been completed. The clinical evidence demonstrates that eladocagene exuparvovec provides sustained improvements in key outcomes in AADC deficiency, including key motor milestones, PDMS-2, AIMS-II, Bayley-III and body weight.

B.2.12.4.1. Strengths of the evidence base

- **All trials were appropriately designed considering the ultra-rare and severe nature of AADC deficiency:** All three clinical trials were single-arm non-RCTs but were appropriately designed and meet the requirements of quality assessment criteria. Each study prospectively and transparently collected data on key outcomes (e.g. PDMS-2, AIMS, Bayley-III) in line with pre-determined standardised protocols. All three studies were similar in design and outcomes, ensuring consistency across studies. The wide selection of outcomes measures ensures outcomes relevant to AADC deficiency were comprehensively captured. The recording and measurement of AEs and mortality across the trials was also thorough and in line with reporting standards. Thus, while the studies have limitations inherent with single-arm studies for ultra-rare conditions, appropriate measures were taken to ensure the quality of the studies.
- **All trials consistently report rapid, significant, and durable benefits with eladocagene exuparvovec across all outcomes:** Across all three studies, treatment with eladocagene exuparvovec was associated with rapid, durable, and significantly improved motor milestone achievement and function, development, cognition, body weight, neurologic outcomes, and dopamine production. And throughout the other measures. The sustained results bolster the confidence in the conclusions from the studies. Safety results were also similar across the trials, with few treatment-related AEs and no treatment-related deaths.
- **There is long-term follow-up in two of the trials:** There was at least five years of follow-up for AADC-CU/1601 and AADC-010 and one-year of follow-up for AADC-011, providing a substantial evidence base and comprehensive data on long-term outcomes. The length of follow-up is considerable when considering the ultra-rare nature of the disease.

B.2.12.4.2. Limitations of the evidence base

While the evidence base for eladocagene exuparvovec clearly demonstrates the clinical and safety value of the treatment, there are some limitations inherent with trials for such a rare and severely debilitating paediatric condition.

- **Low sample size:** The evidence base includes just 28 patients. This is unsurprising given the ultra-rare nature of AADC deficiency, with just [redacted] expected to be diagnosed each year in the UK.[5] It should be noted that the trials supporting eladocagene exuparvovec included approximately 10% of all patients with AADC deficiency worldwide.
- **Ethnicity of population in trials:** All studies were conducted in Taiwan and therefore included an Asian population. This is to be expected given that AADC deficiency is most prevalent in Asia (especially Taiwan/Japan) due to a Founder effect.[2,6] Notably, UK clinical experts agreed that ethnicity is not expected to be a key covariate in determining outcomes in AADC deficiency or following treatment with eladocagene exuparvovec.[5] Aside from the clear difference in race/ethnicity of the patient population, UK clinical experts agreed that the baseline characteristics and demographics in the clinical studies were representative of the patients that they manage in the UK, and therefore it is considered that the trials are broadly generalisable to UK clinical practice.[5]
- **Single-arm studies:** Another limitation is the open-label, non-RCT and single-arm nature of the studies. This is expected with the ultra-rare and severe nature of AADC deficiency where there are no licenced treatments available, making the inclusion of control arm challenging for ethical reasons. However, the feasibility of an ITC was explored further (see section B.2.9 for further details).

B.2.12.5 Relevance of the evidence base to scope

The eladocagene exuparvovec evidence base directly addresses all the key outcomes identified in the NICE scope. All clinical studies supporting eladocagene exuparvovec are within its marketing authorisation for treating AADC deficiency and cover outcomes specified in the scope: mortality, motor function (where applicable age-appropriate motor milestones such as sitting, standing, and walking), autonomic nervous system functioning, speech and language development, cognitive development, body weight, mortality, and adverse effects. The clinical studies did not measure HRQoL outcomes, so HRQoL in this NICE submission were elicited through other methods (See Section B.3.4).

To assess the clinical outcomes, suitable primary and secondary outcomes were recorded, including PDMS-2, AIMS, Bayley-III, body weight, neurologic examination findings with respect to muscle tone (i.e., floppiness), OGC episodes, dystonia, muscle power, deep tendon reflex response, neurotransmitter metabolites in the CSF, and putaminal F-DOPA PET signal.

To assess safety outcomes, the evidence base includes all adverse events, neurological exam findings (excluding muscle tone, OGC episodes, dystonia, muscle power, and DTR response), and viral shedding across the clinical trials.

The population in the evidence base was in line with the anticipated marketing authorisation and the population defined in the scope. The expected licensed indication is for [redacted].

B.2.12.6 External validity to patients in routine clinical practice

As described in Section B.2.3.1.1 and Section B.2.12.4, the clinical studies were conducted in Taiwan and therefore included Asian patients only. UK clinical experts stated that patient race would not impact the disease course or response to treatment given that the all patients have a loss-of-function mutation that results in no AADC enzyme activity.[5]

B.2.12.7 Criteria for clinical practice

In UK clinical practice, eladocagene exuparvovec is expected to be used in line with its final licensed indication.[5] Please see section B.1.1 for the details on the licenced indication.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR was undertaken to identify published cost-effectiveness studies relevant to the decision problem (see Section B.1.1). The methods, search strategies and inclusion and exclusion criteria used, along with results for the SLR of cost-effectiveness studies are provided in Appendix G.

Overall, one relevant cost-effectiveness publication (only available in abstract form) was identified based on the selection criteria (see Table 38). As part of the SLR, four publications were identified and reviewed as potentially relevant cost-effectiveness studies at 2nd pass. Three of the publications were excluded as they did not meet the selection criteria; two did not meet the outcomes criteria and one was unavailable in English language online (the article is published in Spanish).

Table 38: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Simons *et al.* (2022)[88]	2022	Markov model consisting of 2 parts: a development phase followed by a long-term phase	N/R	N/R	N/R	N/R

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; N/R, not reported

B.3.2. Economic analysis

As discussed above, one prior cost-effectiveness model has been identified in AADC deficiency. Simons *et al.* (2022)[88] is a published abstract describing a *de novo* cost-effectiveness analysis (CEA) of a gene-replacement therapy compared to best supportive care (BSC), in children with AADC deficiency. A Markov model was used with a lifetime horizon and NHS and social services perspective. The model consists of two parts: the developmental phase, where patients starting from the no-motor function state can progress to other motor milestone states, and a long-term phase based on extrapolations.

The Simons *et al.* (2022) abstract provides a summary of the CEA conducted by the manufacturer and is used as the basis of the CEA presented in this submission. The following section describes the *de novo* CEA in depth, including the patient population, model structure, intervention and comparators included in the analysis.

B.3.2.1 Patient population

The patient population considered in the CEA is patients [redacted]. This is consistent with the final NICE scope, the SmPC, and the pooled population from the three clinical trials for eladocagene exuparvovec (AADC-010, AADC-011, AADC-CU/1601).

The baseline characteristics of the cohort entering the model are representative of the eligible patient population. Patients enter the model at age four years with a weight of 11.1 kg, which is based on the mean age and weight of patients at baseline in the three clinical trials AADC-CU/1601, AADC-010, and AADC-011, and with no motor functioning (i.e. equating to a median PDMS-2 score between 7.50 and 11.50 at baseline, across the three trials).

B.3.2.2 Model structure

B.3.2.2.1. Overview of model structure

The CEA for this NICE appraisal is made up of two phases aligned to the short-term development and long-term disease course of patients with AADC deficiency. In both phases, patients are modelled at a cohort level, with the short-term development phase supported by individual patient-level data from clinical studies for eladocagene exuparvovec.

The CEA is based on five motor milestone health states (from “worst” to “best”): (i) no-motor function, (ii) full-head control, (iii) sitting unassisted, (iv) standing with support, and (v) walking with assistance. Motor milestone health states reflect motor and development milestones seen in the clinical trials for eladocagene exuparvovec. The worst health state, “no-motor function”, is based on untreated AADC deficiency patients who are bedridden. The best health state, “walking with assistance”, is based on the best outcome seen for patients with the severe phenotype. Although there have been a few cases reported in literature where patients have developed the ability to walk independently following gene-replacement therapy, these patients had the moderate phenotype.[59] All patients with AADC deficiency enter the model in the “no-motor function” health state.

While motor milestone achievement is the key outcome, AADC deficiency also impacts other functions, such as cognition, behaviour, movement, and OGC. In this CEA, improvements in cognitive function and other AADC deficiency related symptoms are implicitly captured within the improvement in motor milestones. Simons *et al.* 2021[89] reported strong correlation between patients’ motor milestone attainment and their cognitive skills (Pearson’s correlation coefficient estimate was 0.83), and PDMS-2 score (Pearson’s correlation coefficient estimate was 0.86). Simons *et al.* 2021[89] then reported that 93% of clinicians (N=21) agreed with the correlation between cognitive and motor skills and their cognitive skills. The approach of using motor milestone health states has also been validated extensively with clinical experts (clinical advisory board 1[26] and 2[24], UK clinical expert consultations,[5] and clinician survey[25]) and was considered a valid modelling approach by health economics and outcomes research (HEOR)

experts (Economic advisory board).[54] For more information on expert validations, please see Section B.3.14.

The two phases in the model are as follows:

- **A development phase** tracks the development of a patient with AADC deficiency from the "no-motor function" health state to the higher motor milestones (e.g., standing with support). The duration of the developmental phase in the base-case CEA is 12 years, designed to capture the length of time during which a normal child would develop as well as the long-term improvements associated with eladocagene exuparvovec.

  In the eladocagene exuparvovec arm of the CEA, the achievement of motor milestones is based on individual patient-level PDMS-2 scores from the AADC-010, AADC-011, and AADC-CU/1601 trials (for more information on the appropriateness of the PDMS-2 scale, please see Section B.3.2.2.7).[16,18,17] Given the heterogeneity in length of follow-up for each patient's PDMS-2 scores in trials for eladocagene exuparvovec (two patients were followed up for up to 108 months), individual patient PDMS-2 scores are extrapolated in the development phase using a Bayesian growth model. A cumulative ordered logit model, using the estimated PDMS-2 scores as a covariate, is then used to predict each patient's motor milestone achievement during the 12-year development phase. Each patient's motor milestone achievement at the end of the development phase is then taken into the *long-term phase*. For more details on the Bayesian growth model and cumulative ordered logit models, see Section B.3.3.1.1.1.

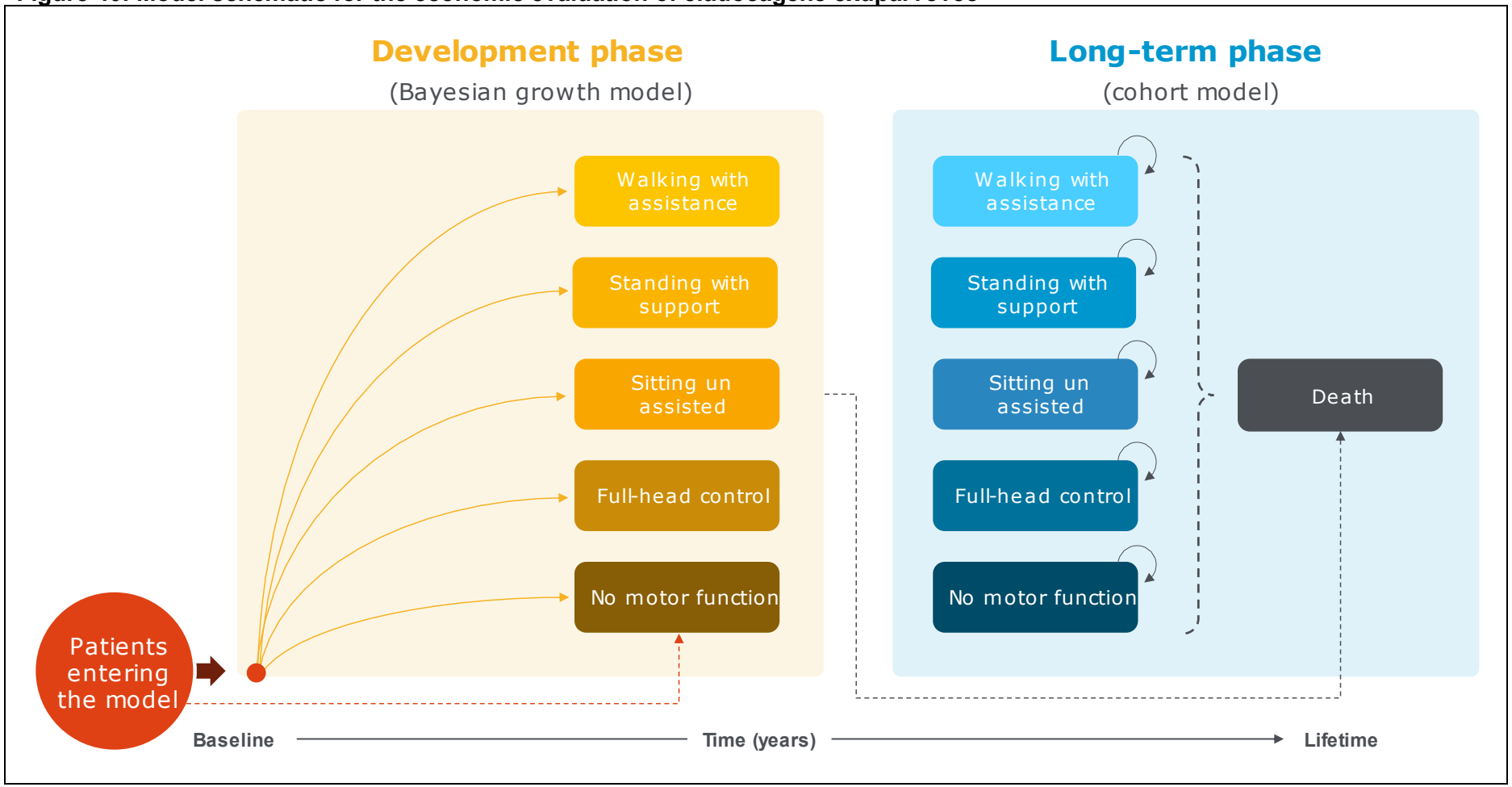
  The BSC arm is based on a natural history database (NHDB) compiled by PTC through an SLR that identified all patients with AADC deficiency in the literature.[8] A total of 237 unique subjects were identified in the literature of which high quality data was available for 185 of them. Among these patients, 49 had attained no motor milestones by 24 months of age and were therefore assumed to have severe AADC deficiency (i.e. similar profile to patients in trials for eladocagene exuparvovec, as confirmed with a UK clinical expert[5]). Further details on how the NHDB was generated is presented in Section B.2.9. For more details on the results of the NHDB that are used in the CEA, see Section B.3.3.2

- **The long-term phase** uses static health states, with patients staying in the motor milestone health state achieved during the *development phase* until death. Based on the motor milestone health state achieved in the *development phase*, patients in each health state are attributed a probability of mortality (based on parametric survival curves) and a health state utility value and health state management costs. Due to the very limited literature related to the survival of patients with AADC deficiency (see details in Section B.3.3.2), survival curves are based on a cerebral palsy (CP) proxy using survival distributions reported by Brooks *et al.* (2014).[92] The use of CP as a proxy for AADC deficiency when deriving survival estimates has been validated with global clinical experts at an advisory board (Clinical advisory board 1[26]), UK clinical experts during validation of this NICE submission (April 2022)[5], and a clinician survey[25]. For

more details regarding the derivation of survival estimates for patients with AADC deficiency, see Section B.3.3.2.

The structure of the model is shown in Figure 40. The model concept, structure, approach to global symptom improvement, and UK base-case have been validated with clinicians (Clinical advisory board 1[26] and 2[24], UK clinical expert consultations[5] and clinician survey;[25] see Section B.3.14 for details of advisory boards and consultations).

Figure 40: Model schematic for the economic evaluation of eladocagene exuparvovec



Each patient enters the model at baseline with no-motor function. After receiving BSC or eladocagene exuparvoevc at baseline, the patient transitions through the motor milestone states, modelled using Bayesian growth models and the cumulative ordered logit model, for the duration of the developmental phase. In the base-case CEA, the developmental phase is 12 years. After the developmental phase, the patient enters the long-term phase modelled using a cohort model. The patient is expected to sustain their motor milestone achievement and it is assumed that they will not shift motor milestones state.

B.3.2.2.2. Model conceptualisation

To inform the CEA design and structure, a targeted review of NICE appraisals for rare or ultra-rare indications was conducted. The review focused on NICE appraisals related to neuromuscular diseases or gene-replacement therapy, including adenosine deaminase deficiency-severe combined immunodeficiency (Strimvelis; HST 7)[93], Duchenne muscular dystrophy (ataluren; HST 3)[94], mucopolysaccharidosis type IVa (elosulfase alfa; HST 2)[95], inherited retinal dystrophies caused by RPE65 gene mutations (voretigene neparvovec; HST 11)[96], spinal muscular atrophy (SMA; onasemnogene abearvovec, HST 15; nusinersen, TA588)[97,98], and metachromatic leukodystrophy (atidarsagene autotemcel; HST ID1666)[99].

Notably, HST 15 (onasemnogene abearvovec in SMA, HST 15)[97] used a five health-state model framework (from "no motor function" to "walking with assistance") with a short-term phase (based on observed data) and a long-term cohort extrapolation phase. Similar to AADC deficiency, motor milestones are considered the main clinical outcome to measure outcomes in patients with SMA.

Following the review of similar NICE appraisals, approaches to the model structure and outcomes were discussed in a series of clinical and economic validations (see Section B.3.14 for details of advisory boards and consultations),[24–26,53] to ensure that the CEA structure was optimal in capturing the disease course and outcomes in patients with AADC deficiency.

B.3.2.2.3. Rationale for a cohort model over a patient-level simulation model

Based on clinical trial evidence and clinician input, there is considerable heterogeneity in outcomes of AADC deficiency patients. For this reason, a patient-level simulation modelling approach was also considered as a potential option for this CEA, as it could allow a range of different symptoms to manifest simultaneously, characterising the full burden of disease in patients. Upon consideration, a cohort model approach was considered more appropriate than a patient-level simulation for this CEA because:

- **Patient-level simulation modelling is data-intensive:** A patient-level simulation modelling method simulates one patient at a time and would allow for a patient's path through the model to be dependent on their history. As patients are tracked individually, patient-level simulation models require a large amount of data for individual patient characteristics.
- **Patient-level simulation modelling has high computational requirements:** NICE DSU guidelines (NICE TSD 15)[100] recommend that a large number of simulations are carried out to compute patient-level simulation model outcomes appropriately. Assessing input parameter uncertainty for all simulations means that patient-level simulation models have a high computational burden.
- **Patient-level simulation modelling requires an understanding of the relationship between individual outcomes for a disease**: For example, the relationship between motor development, cognitive function, OGC, and body weight. Given the limited data

in AADC deficiency in general, an ultra-rare condition, the relationship between outcomes have not yet been established.

Thus, based on the limited data available, the complexity and computational burden of the patient-level simulation and the need for a clear understanding of the full relationships between various symptoms, the patient-level simulation approach is not optimal or feasible for modelling AADC deficiency. A cohort approach is more appropriate than a patient-level simulation approach as it is more transparent and less data-intensive and is therefore less reliant on assumptions and/or suboptimal data values. As discussed in Section B.3.2.2.5, the cohort approach can capture the substantial heterogeneity seen in patient outcomes through the data analytics included in the development phase estimating distribution of the validated PDMS-2 scores.

B.3.2.2.4. Rationale for a development phase and extrapolation phase

Clinical data indicate that some patients with AADC deficiency, treated with eladocagene exuparvovec, experience a plateau in the development of their motor milestones over time. Thus, a development phase in which patients achieve motor milestones over the short-to-medium term is appropriate as it aligns with the clinical data. Similarly, an extrapolation phase, whereby patients remain in the same motor milestone health state for the long-term, reflects the clinical data. Furthermore, this captures the durability of the response seen in the trials (see Section B.2.6), whereby patients maintain their milestone once they reach it, whilst also establishing a conservative perspective as it assumes no future progression (only death). The model structure was validated in an economic advisory board, where all eight experts agreed that the model structure was suitable (see Section B.3.14 for details of discussion).[53,101]

B.3.2.2.5. Rationale for a cohort model over a Markov model

Previous NICE appraisals for similar diseases to AADC deficiency (e.g. Strimvelis [HST 7][93], onasemnogene abearvovec [HST 15][97] and nusinersen [TA588][98]) use a Markov model (with transitions) to model five motor milestone health states. A Markov approach was therefore considered for this CEA given its importance as a clinical outcome.

In this CEA for AADC deficiency, a cohort model approach with (i) Bayesian development phase followed by (ii) long-term phase is better aligned to the data informing the analysis than using a Markov approach, which relies on transition probabilities:

- **A cohort model approach maximises the use of available data:** In trials for eladocagene exuparvovec (AADC-CU/1601, AADC-010, and AADC-011 trials), the primary efficacy endpoint is PDMS-2.[16,18,17] The PDMS-2 scale has a total score ranging from 0-250. The Bayesian development phase maximises the use of the PDMS-2 data to predict the short-term trajectory of patients whose PDMS-2 score at last follow-up places them in between motor milestone health states. By being able to fit motor milestone states to extrapolated PDMS-2 scores, the CEA is able to capture progression and improvements within motor milestone states. A Markov model would not leverage the trial PDMS-2 data as well as the two-phase cohort model.

- **A cohort model approach more accurately reflects the data underpinning development in children with AADC deficiency:** This CEA uses PDMS-2 scores to map the development of patients with AADC deficiency. The PDMS-2 scores are then used to derive motor milestone health states. A Markov approach would only consider patients in their motor milestone states rather than first modelling/extrapolating PDMS-2 scores to derive the motor milestone health state. The Markov model would therefore disregard key motor development scoring data (PDMS-2 scores).
- **A cohort model approach avoids complicated transition probabilities:** Markov models may be simple when implementing constant transition probabilities. AADC deficiency patient motor development can be considered non-linear as patients demonstrate improvements in motor function which plateaus in the long-term. Therefore, to fit the data to a Markov model, time-dependent transition probability matrices would be needed. This would prove to be challenging with clinical evidence from the trials (AADC-CU/1601, AADC-010, and AADC-011) given the unpredictability and heterogeneity in patient outcomes and the loss of follow-up in certain cases.
- **A cohort model approach is more transparent:** Predicting the motor milestones of patients using time-dependent transition matrices in a Markov model instead of extrapolated PDMS-2 scores lacks transparency when analysing the data. When interrogating a model of this nature, it can be challenging to understand how the fitted versus observed motor milestone distributions are generated because of lack of data.

Thus, a cohort approach, which omits Markovian assumptions and predicts patient motor milestone trajectory using PDMS-2 scores, is more appropriate than a Markov approach, as it maximises the use of the data, more faithfully reflects the data generating process, and transparently demonstrates the distribution of extrapolated data over time.

Overall, given the heterogeneity in outcomes and challenges in extrapolating data where there is missingness and non-linear development, the most appropriate model framework for this appraisal for AADC deficiency uses motor milestone health states and includes a growth model development phase and a long-term extrapolation phase.

B.3.2.2.6. Rationale for motor milestone health states

Motor development delay is one of the most important consequences of AADC deficiency. Without gene-replacement therapy, almost all patients with a severe case of AADC deficiency do not achieve any motor function and remain bedridden during their whole life, with complete dependence on their carers.[6] In the three clinical trials for eladocagene exuparvovec (AADC-CU/1601, AADC-010, and AADC-011), the primary efficacy endpoint was the achievement of key motor milestones assessed using PDMS-2. In AADC-010, for example, the primary efficacy variables were the proportion of patients who achieved the following milestones: full head control, sitting unassisted, standing with support, and walking with assistance. Motor milestones have been identified as the most important outcome by international and UK clinical experts (Clinical advisory board 1, February 2020; consultation with UK clinical experts,

April 2022).[5,26] Furthermore, Wassenberg *et al.* (2017) identified movement dysfunction to be the most common disorder associated with AADC deficiency[2] and Hwu *et al.* (2017)[6] identified motor dysfunction to be a significant component of AADC deficiency. Therefore, the CEA uses motor milestones as health states as it aligns with the primary outcome in clinical studies for eladocagene exuparvovec and is a key outcome in AADC deficiency.

B.3.2.2.7. Rationale for using PDMS-2 to predict motor milestones

As described in Section B.3.3.1.1.1, the CEA uses established statistical models to predict motor milestone achievement based on observed trial PDMS-2 data for individual patients. This approach overcomes challenges with the small sample size, heterogeneous patient trajectories, and different lengths of follow-up data for some patients (e.g. 3 patients treated with eladocagene exuparvovec in AADC-011 have 12 months of follow-up data, whereas 2 patients in AADC-CU/1601 have 9 years of follow-up data).

As described in Section B.2, PDMS-2 is an important and validated tool used to measure motor function in infants. It is a skill-based measure of gross and fine motor development, administered to children from birth.[49] It has four gross motor subtests (reflexes, stationary, locomotion, object manipulation) and two fine motor (grasping, visual-motor integration) subtests.[6] PDMS-2 is a key outcome for AADC deficiency and this CEA because:

- **PDMS-2 was the primary endpoint measure in trials for eladocagene exuparvovec:** International consensus clinical guidelines for AADC deficiency do not discuss preferred measures for assessing patient motor function. In the absence of a preferred instrument, PDMS-2 was used as the primary endpoint in trials for eladocagene exuparvovec and was used to determine motor milestones in the trials. PDMS-2 is more sensitive than using motor milestones alone as it provides granular information and can therefore detect small changes in motor function.
- **There are benchmark PDMS-2 data for patients with AADC deficiency:** PDMS-2 was a key endpoint measure in Chien *et al.* (2017), which described the natural history of 37 patients with AADC deficiency in Taiwan.[6] PDMS-2 was used as it is provides granular evidence of motor dysfunction. Of the 22 patients with PDMS-2 data, the median total raw PDMS-2 score was below the first percentile for normal children of the same age.[6] The existence of PDMS-2 data for the general population in Taiwan and for the AADC deficiency natural history population[6] means there are important benchmark values to compare to when considering the efficacy of new therapies for AADC deficiency. AADC deficiency natural history data for other motor development instruments (e.g. GMFM-88) do not exist in the literature.
- **PDMS-2 can be administered to children from birth:** Unlike other scales (e.g. AIMS, Gross Motor Function Measure (GMFM), Movement Assessment Battery for Children, Motor Function Measure, Paediatric Evaluation of Disability Inventory, Test of Gross Motor Development), PDMS-2 can be applied right from birth and allows a complete analysis of global and fine motor skills.[49]

- **PDMS-2 is widely used to measure motor function for other conditions**: including those with similarities to AADC deficiency. PDMS-2 was accepted by NICE as an appropriate instrument to measure motor function in studies that informed the NICE 2016 clinical guideline on the diagnosis and management of CP,[102] and was shown to have good test-retest reliability, responsiveness, and sensitivity to change in a study exploring its validity in CP.[49,103] It has been used in CP, autism, Down syndrome, Hurler syndrome, and to explore the effects of biological (e.g. prematurity, malnutrition) and environmental (e.g. socioeconomic status, family routine) variables on normal child development.[49] It has also been validated in various populations across various geographies.[49]

- **A systematic review identified PDMS-2 as having excellent validity and test-retest reliability:** In a 2018 comparison of instruments to measure child gross motor function, PDMS-2 was noted as the only measure that is sensitive to partial mastery of a task and one of only four tools with a reported minimum clinically important difference (MCID) with satisfactory sensitivity and specificity. It was also noted as having high internal consistency, excellent test-retest reliability, satisfactory sensitivity, and thorough content validity. The authors concluded that PDMS-2 is among the most reliable assessments for gross motor function in children.[104]

B.3.2.2.8. Rationale for global symptom improvement

While health states in this CEA are based on motor milestones, patients with AADC deficiency experience a wide-range of symptoms (e.g., cognitive defects, excessive crying, OGC, dystonia, as detailed in Section B.1.3.1). To ensure the CEA captures the wide-ranging symptoms of AADC deficiency in a way that is most representative of the disease in the clinical setting, the relationship between global symptom improvement with each motor milestone health state was explored.

For this CEA, it has been assumed that other symptoms of AADC deficiency improve in parallel with improvements in motor function. This was based on:

- **Global symptom improvement is observed in patients with AADC deficiency:** Evidence in patients with AADC deficiency post-gene-replacement therapy[59] indicates that patients experience global symptom improvement from baseline, including improved motor functioning, dystonia, OGC, autonomic dysfunction, mental status and sleep disturbance. Given cognitive development delay is a key outcome in AADC deficiency, the specific link between motor and cognitive development in AADC deficiency was explored in more detail for this appraisal. In the three eladocagene exuparvovec trials, there was a high positive correlation between cognitive development and motor milestone achievement, and PDMS-2 and Bayley-III. This highlights that improvements in motor milestones broadly correlate with improvements in other symptoms of AADC deficiency. Further details on the correlation between motor and cognitive development is presented in Appendix J.

- **Global symptom improvement reduces uncertainty and overcomes the complexity and data challenges with a patient-level simulation modelling approach:** A patient-level simulation approach would require motor function, cognitive development and various other symptoms to be modelled separately. As discussed in Section B.3.2.2.3, a patient-level simulation is not appropriate for AADC deficiency as it is too data-intensive and the ultra-rare nature of AADC deficiency means the data required to populate the analyses are not available.
- **Experts agreed that eladocagene exuparvovec evidence indicates global symptom improvement:** UK clinical experts agreed that they would expect other AADC deficiency symptoms to improve as motor development improved. Please see Section B.3.14 for more details on the advisory boards. In addition, all eight HEOR experts believed that the evidence presented in Simons *et al.* 2021 was indicative of global symptom improvement.
- **Global symptom improvement is observed in similar conditions to AADC deficiency:** Due to the rarity of the condition, there is very limited published information on the relationship between motor milestones and other AADC deficiency symptoms. There is, however, a relationship between motor function and other symptoms in neurological conditions similar to AADC deficiency (including CP,[105] SMA,[106,107] and global developmental delay [GDD[108]]).[107,109] Dusing *et al.* (2019)[105] demonstrated significant improvements in both motor functioning and cognitive skills in a child with CP diagnosed with hypoxic ischaemic encephalopathy at birth, following the introduction of physical therapy. In SMA Type I, Polido *et al.* (2019)[106] found that poorer cognitive performance was more frequently observed in patients with severe disease compared to more moderate forms of the disease. Dunaway *et al.* (2012)[107] hypothesised that, based on prior research, increasing locomotion earlier during childhood allows patients to develop in other aspects e.g., psychological, behavioural, and cognitive aspects. Furthermore, use of symptom correlations with motor milestones has been accepted by NICE in a previous appraisal.[110]

B.3.2.2.9. Summary of key clinical sources and parameters

The CEA captures key evidence, variables and parameters related to AADC deficiency and in line with the clinical evidence supporting eladocagene exuparvovec. The clinical sources and parameters are summarised as follows (further details can be found in Section B.3.3):

- **Motor milestone achievement:** For eladocagene exuparvovec, PDMS-2 scores are taken from trial data (AADC-CU/1601, AADC-010, and AADC-011) to estimate the achievement of motor milestones. Bayesian growth models are used to extrapolate long-term PDMS-2 scores. A cumulative ordered logit model with estimated PDMS-2 scores as a covariate is then used to predict patient motor milestone achievement. As eladocagene exuparvovec was studied in single-arm trials, there was no control arm. Motor milestone achievement in the BSC arm of the CEA is informed using a NHDB compiled through a literature review of all known cases of AADC deficiency in the

literature. An ITC has been explored to evaluate the feasibility of conducting analyses to generate sufficiently robust estimates for the comparative effectiveness of eladocagene exuparvovec compared to BSC. See Section B.2.9 for more details regarding the ITC feasibility assessment.

- **Safety:** Data for the eladocagene exuparvovec arm in the CEA were taken from clinical trials for eladocagene exuparvovec (see Section B.2.10). Only moderate or severe TEAEs were included in this CEA due to their assumed impact on QoL and associated costs. AE data are not considered for the BSC cohort due to a lack of literature and evidence. It is assumed that TEAEs in the BSC arm are captured in patients' disease management resource use costs.

B.3.2.2.10. Summary of HRQoL sources and parameters

HRQoL data for AADC deficiency patients are limited and were not captured in the clinical trials. Clinical experts have highlighted that EQ-5D is not sensitive enough to capture the cognitive limitations associated with the disease.[26] For this CEA, HRQoL data were elicited using a time trade-off (TTO) study by Smith *et al.* (2021)[27] based on five motor milestone health state vignettes (developed by Hanbury *et al.* [2021][56]) aligned to the motor milestone health states in the CEA and each capturing motor function, cognitive function, OGC, and other aspects of AADC deficiency. A TTO approach is recommended among the hierarchy of preferred HRQoL methods published in the NICE health technology evaluations manual (2022)[23] and the NICE DSU technical support document 11[111], which states that TTO is the preferred method for collecting HRQoL data when EQ-5D is not appropriate. Furthermore, the vignette/TTO approach is in line with the vignette approach accepted by NICE in previous HSTs (e.g. voretigene neparvovec; HST 11)[96]. More detail on the health state utility values (HSUV) and estimation of the values is presented in Section B.3.4.5 .

Disutilities associated with adverse events, caregivers and caregiver bereavement were also included in the base-case of the CEA. More detail can be found in Section B.3.4.4**.**

B.3.2.2.11. Summary of cost and resource use parameters

The CEA captures various healthcare costs and resource use. As neither NICE nor NHS England have any clinical guidelines specific to the management AADC deficiency, treatments and healthcare resource use for patients with AADC deficiency are informed using a consensus guideline by Wassenberg *et al.* (2017).[2] The CEA assumes that BSC treatment and resource use is dependent on the motor milestone health state of the patient; patients in both the eladocagene exuparvovec arm and the BSC arm receive BSC treatments/healthcare resources. To capture the differences in cost and resource use in the eladocagene exuparvovec and BSC arms of the model, the proportion of patients receiving each BSC therapy differs across each motor milestone state. This approach was validated with clinical experts with experience in AADC deficiency.[24]

The specific BSC treatment regimens included in the CEA are based on publications by Wassenberg *et al.* (2017)[2] and Brun *et al.* (2010).[15] The BSC basket composition for each

motor milestone is generated based on a clinician survey for AADC deficiency carried out by Saberian *et al.* (2021).[112] Associated unit costs for BSC therapies are sourced from the British National Formulary (BNF)[113] for 2021 costs. The CEA assumes that BSC therapies do not incur an administration cost.

Annual resource use inputs are also sourced from a clinician survey carried out by Saberian *et al.* (2021)[112] and associated costs are sourced from the National Schedule of Reference Costs 2019/2020[114] and the Unit Costs of Health and Social Care 2020 report by the Personal Social Service Research Unit (PSSRU).[115]

Costs associated with eladocagene exuparvovec, including gene-replacement therapy acquisition and administration costs are included. Moderate or severe TEAEs associated with eladocagene exuparvovec are also included in the CEA. Four TEAEs were considered: dyskinesia, pneumonia, gastrointestinal disorders, and gastroenteritis. The associated costs for the TEAEs are sourced from National Schedule of Reference Costs 2019/2020.[114] For more detail on the costs and resource use included in the CEA, see Section B.3.5.

B.3.2.2.12. Model specification

The model uses a lifetime horizon to reflect the life-long nature of AADC deficiency. The model therefore captures the full costs and benefits over the survival time of all patients modelled. This aligns with the NICE manual for health technology evaluations (2022).[23]

The model uses a 3-month cycle length. This cycle length is considered sufficient to accurately capture the clinical outcomes reported for patients with AADC deficiency in the clinical trials. This is also in alignment with timepoints of outcomes measured in the trial and validated with clinical experts. A half-cycle correction is applied.

The CEA uses a 1.5% discount rate for health effects and costs, instead of the standard 3.5% discount rate. According to the NICE health technology evaluation manual (2022)[23] the use of a 1.5% discount rate is acceptable when three criteria are met. Table 39 **o**utlines the justification for the 1.5% discount rate in the base case.

Given the evidence that eladocagene exuparvovec offers significant QALY gains over the limited BSC offered in standard practice, a 'QALY-modifier' is applied in the base case CEA. This is line with the NICE health technology evaluations manual (2022).[23]

The model specifications are presented in Table 40.

Table 39: Rationale for the use of a 1.5% discount rate for this appraisal

	NICE 1.5% discount rate criteria (2022)[23]	**Explanation of how the criteria is met for eladocagene exuparvovec in AADC deficiency**
1	The technology is for people who would otherwise die or have a very severely impaired life.	AADC deficiency clearly meets this criterion: • AADC deficiency is a fatal disorder, often resulting in death in the first two decades of life. Based on the limited available published data[2,6,7] and clinical expert consultations, it is expected that most patients with severe AADC deficiency die by the time they are teenagers.

		• The severe and wide-ranging symptoms suffered by patients with AADC deficiency leave them bedridden with no motor function and dependent on round-the-clock care for their whole lives. • Natural history publications (Hwu *et al.* 2017)[6] and the natural history database (Bergkvist *et al.* 2021)[8] show that over 95% of patients with severe AADC deficiency fail to achieve any motor milestones in their lifetime. • Alongside no motor function, patients suffer from movement disorders, hypokinesia, dystonia, oculogyric crisis, behavioural problems, autonomic dysfunction, developmental delays, and language and cognition issues.[68]
2	It is likely to restore them to full or near-full health.	Eladocagene exuparvovec meets this criterion: • Following eladocagene exuparvovec, patients improve from having no motor function to achieving clinically meaningful motor milestones. Improvements are rapid (from as early as three months) and sustained across all symptoms measured in clinical studies (See Section B.2.6). • As demonstrated in videos in Tai *et al.* (2022),[68] three patients aged 2.5, 4.2, and 2.0 years at baseline, respectively, could walk freely without assistance just 2.9, 2.4 and 2.2 years after receiving eladocagene exuparvovec. These life-changing improvements were sustained, with one patient able to run freely 5 years after gene-replacement therapy. Life-changing improvements were also seen in other areas of development, with one patient able to talk 3.4 years after gene-replacement therapy and having similar language skills to a 3-year old when aged 5 years.[68] • While survival data from the trials for eladocagene exuparvovec are currently immature, data in Tai *et al*. (2022) shows that seven patients treated with eladocagene exuparvovec were above the age of 13 years at a 31 December 2020 data cut, with one patient aged 16.6 years of age.[68] This indicates that gene-replacement therapy may prolong patient survival. Furthermore, higher motor milestones are associated with longer survival, as demonstrated in the survival estimates for AADC deficiency presented in Table 44, Section B.3.3.2. As eladocagene exuparvovec is associated with significant improvement in motor milestones (Table 41, Section B.3.3.1), patients treated with eladocagene exuparvovec are likely to have considerably longer survival and improved quality-of-life than patients receiving BSC. • The truly transformative and health-restoring benefits of eladocagene exuparvovec are best illustrated in a video provided in Tai *et al.,* (2022)[68] and in the video provided by PTC as part of the EMA Scientific Advisory Group meeting,[19] which shows a patient able to walk, run, and talk just a few years after gene-replacement therapy. In a TTO study, members of the UK general population rated the “walking with assistance” AADC deficiency motor milestone health state vignette (which also described other characteristics of AADC deficiency) as having a utility of 0.728.[27] This is comparable to UK general population mean utility of 0.868 in adults (EQ-5D).[116]
3	The benefits are likely to be sustained over a very long period.	Eladocagene exuparvovec meets this criterion: • As reported in Section B.2.6, eladocagene exuparvovec is associated with transformational and durable improvements that continue beyond five years after treatment in children with AADC deficiency, restoring them to near-full health and allowing them to live a more functional life. • As shown in patient videos in Tai *et al.* (2022)[68] and in a video of another patient provided to the EMA during the regulatory appraisal,[19] patients can run without assistance five years after receiving eladocagene exuparvovec.

		• Among patients in AADC-CU/1601 with over 5 years of follow-up (6-10 years) reported in Tai *et al.* (2022), PDMS-2 scores were sustained and in some patients were continuing to improve,[68] highlighting the life-long benefits of gene therapies in patients who would live their entire shortened life with no motor function and very poor quality-of-life.

Abbreviations: EQ-5D – EuroQol 5-dimensions; NICE – National Institute for Health and Care Excellence

Table 40: Features of the economic analysis: eladocagene exuparvovec in AADC-deficiency

Factor	Chosen values	Justification
Time horizon of model	Lifetime horizon	NICE reference case.[23] NICE recommends a time horizon to reflect the differences between costs and outcomes between alternative technologies. In order to reflect the life-long nature of AADC deficiency, the base-case model time horizon is lifetime, allowing full costs and benefits over the survival time of all patients modelled to be captured.
Cycle length	3-month	This cycle length is considered sufficient to accurately capture the clinical outcomes reported for patients with AADC deficiency in the clinical trials. This is also in alignment with timepoints of outcomes measured in the trial and with clinician opinion (Clinical advisory board 1, February 2020)[26] regarding appropriate timepoints for measurement of efficacy endpoints post-gene-replacement therapy. The half-cycle correction is applied.
Discounting for costs	1.5%	NICE reference case.[23]
AADC deficiency treatments		
Intervention	Eladocagene exuparvovec	-
Comparator	BSC	There are currently no licensed disease-modifying therapies for the treatment of AADC deficiency, BSC is the main comparator considered in the CEA.
Model inputs and assumptions		
Clinical effectiveness	Clinical effectiveness is characterised by the motor milestone achievement of a child with AADC deficiency. *Eladocagene exuparvovec:* Motor milestones achievement of patients receiving eladocagene exuparvovec was taken directly from clinical trial evidence. PDMS-2 scores were sourced from the three clinical trials (AADC-CU/1601, AADC-010, and AADC-011 trials)[16,18,17] for eladocagene exuparvovec and further extrapolated using Bayesian modelling. *BSC:* Motor milestones achievement of patients receiving BSC was taken from a NHDB.	*Eladocagene exuparvovec:* Due to the small number of patients and the heterogeneity in the length of follow-up, Bayesian growth models were needed to extrapolate PDMS-2 scores. A cumulative ordered logit model, using PDMS-2 scores as a covariate, is then used to predict motor milestone achievement. The use of both models allowed for the CEA to utilise the full range of clinical data as well as extrapolate results for the full developmental phase. The implementation of the Bayesian growth models and a cumulative growth model was supported and validated in an advisory board with HEOR experts.[54] *BSC:* Eladocagene exuparvovec clinical trials were single-arm studies and therefore did not include a control arm. There is very limited published evidence on patients with AADC deficiency. A NHDB was therefore complied through an extensive literature review of all published

		reports of patients with AADC deficiency. The NHDB was created as part of the EMA regulatory approval process and was externally validated by eight HEOR experts.[54] The use of a NHDB natural history cohort has been accepted in previous NICE HST submissions for onasemnogene abeparvovec (HST 15)[97] and atidarsagene autotemcel (ID1666).[99]
Safety	Moderate and severe TEAE data were sourced from the three clinical trials for eladocagene exuparvovec (AADC-CU/1601, AADC-010, and AADC-011 trials)[16,18,17]. AEs associated with BSC are not included in the CEA.	Moderate and severe AEs are included in the model due to the impact on associated costs and the patients QoL. Moderate-to-severe TEAEs affecting ≥20% of patients within the first 12 months of follow-up were included (dyskinesia, pneumonia, gastrointestinal disorders and gastroenteritis). Corresponding TEAE data for patients in the BSC cohort were not included in the CEA due to lack of data. It is therefore conservatively assumed that AE costs for the BSC arm are captured as part of the disease management costs.
Source of utilities	Patient QoL Utility values from a UK TTO study by Smith *et al*[27] use specific vignettes. Utility values were derived for each motor milestone: • No-motor function – 0.494 • Full-head control – 0.537 • Sitting unassisted – 0.631 • Standing with support – 0.676 • Walking with assistance – 0.728 Caregiver QoL Caregiver disutility values are taken from the study by Acaster *et al.* (2013)[28]. Utility values are given for each motor milestone: • No-motor function – 0.09 • Full-head control – 0.09 • Sitting unassisted – 0.03 • Standing with support – 0.03 • Walking with assistance – 0.00 Adverse events QoL The TEAE disutility values are based on published literature. The duration of the events was assumed to be (60 days) in the model due to the absence of data from the literature. Bereavement QoL	No HRQoL data was collected from clinical trials and the EQ-5D was considered not appropriate for the collection of HRQoL data. A TTO study using health state vignettes was conducted to elicit utility values. Use of vignette study to elicit utility values is in line with hierarchy of preferred HRQoL evidence published in the NICE health technology evaluations manual (2022)[23]. The use of TTO study in the base case is in line with the guidance of the NICE DSU technical support document 11[111] and in line with hierarchy of preferred HRQoL evidence published in the NICE health technology evaluations manual (2022)[23]. Caregiver disutility values were taken from the NICE submission for elosulfase alfa (HST 2)[95]. The study by Acaster *et al.* (2013) [28] provides EQ-5D utility decrements associated with caregivers of patients with multiple sclerosis. See Section B.3.4.5 for more detail of utilities.

	An average of the disutility values from the study by Song *et al.* (2010)[117] is applied in the CEM - 0.037.	
Source of costs	Intervention and comparator treatment costs: Treatment acquisition costs for eladocagene exuparvovec were included. BSC treatments and dosing were sourced from Wassenberg *et al.* (2017)[2] and Brun *et al.* (2010).[15] Usage of BSC therapies per motor milestone state are based on results from a clinician survey from Saberian *et al.* (2021)[112]. The unit cost of BSC therapies is sourced from the British National Formulary.[113] Treatment administration costs: Captures the cost of pre- and post-operative care associated with the administration of eladocagene exuparvovec, using NHS Reference Costs (2019/20).[118] Disease management costs: Costs for follow-up visits, medical procedures and technical procedures based on motor milestone achievement was sourced from Saberian *et al.* (2021)[112]. The unit costs of each resource use type is sourced from National Schedule of Reference Costs 2019/2020[114] and Unit Costs of Health and Social Care 2020 report by the Personal Social Service Research Unit (PSSRU)[115]. Adverse event costs: Costs for moderate and severe adverse events were sourced from the Reference Costs 2019/2020[114]	Resource use input was supported by experts in clinical advisory board 2.[24] Associated costs are in line with the NICE reference case. See Section B.3.5 for more details.

Abbreviations: AADC – Aromatic L-amino Acid Decarboxylase; AE – adverse event; BSC – best supportive care; CEA – cost-effectiveness analysis; EMA – European Medicines Agency; HEOR – Health Economics and Outcomes Research; HST – highly specialised technology; NHDB – Natural History Database; NHS – National Health Service; NICE – The National Institute for Health and Care Excellence; PDMS-2 - Peabody Developmental Motor Scale – Section Edition; QoL – quality-of-life; TEAE – treatment-emergent adverse event; TTO – time trade-off; UK – United Kingdom

B.3.2.3 Intervention technology and comparators

B.3.2.3.1. Intervention: eladocagene exuparvovec

Eladocagene exuparvovec is a gene replacement therapy involving an AAV2 capsid containing the human DDC gene (i.e. the gene that encodes the AADC enzyme).[31] The proposed indication for eladocagene exuparvovec is for the [redacted].[31]

Eladocagene exuparvovec is administered by bilateral intraputaminal infusion in one surgical session.[31]

For more information on the product characteristics of eladocagene exuparvovec, please see Appendix C1.1 SmPC). For more information on the efficacy and safety of eladocagene exuparvovec, please see Section B.2.10.

B.3.2.3.2. Comparator: BSC

As there are currently no approved disease-modifying therapies in AADC deficiency, BSC is the main comparator considered in the CEA. BSC provides symptomatic management only to patients with AADC deficiency and comprises symptomatic treatments as well as multidisciplinary team support from specialist (see Section B.1.3.8 for further details).

Based on the Wassenberg *et al.* (2017)[2] consensus guideline described in Section B.2, and in line with the final NICE scope, a basket of therapies is included in the BSC arm:

- First-line symptomatic therapies
- MAO inhibitors
- Dopamine agonists
- Vitamin B6
- Other symptomatic therapies
  - Anticholinergic agents
  - Benzodiazepines
  - Melatonin
  - Clonidine
  - Nasal decongestants

In the CEA, BSC is dependent on motor milestone health state, based on results from a clinician survey in from Saberian *et al.* (2021)[112]. The CEA therefore assumes that patients receiving eladocagene exuparvovec also receive BSC (i.e. as background medical costs).

B.3.3. Clinical parameters and variables

B.3.3.1 Motor milestone achievement (development phase)

B.3.3.1.1. Eladocagene exuparvovec

B.3.3.1.1.1. Using PDMS-2 scores to estimate motor milestones

In the developmental phase of the model, patients achieve motor milestones following treatment with eladocagene exuparvovec and the data are taken from the eladocagene exuparvovec clinical trials. The base-case CEA uses data from a total of 28 patients who received either the $1.8x10^{11}$ vg or $2.4x10^{11}$ vg dose across the three clinical trials for eladocagene exuparvovec (AADC-010, AADC-011, AADC-CU/1601; follow-up times ranging from 12 months to a maximum of 108 months). All 28 patients in the trials were classified as having not reached a motor milestone at baseline.

To model motor milestone achievement following eladocagene exuparvovec in the CEA, analyses were carried out on individual patient motor milestone trajectories over time (these trajectories are depicted in Figure 58 in Appendix J). As can be seen in Figure 58 in Appendix J the average overall patient motor milestone trajectory is not clear due to the small sample size and heterogeneity in motor milestone achievement over time. This makes extrapolation in the CEA difficult using just the observed trial data.

To overcome the challenge of high heterogeneity in motor milestone trajectory among patients treated with eladocagene exuparvovec, other patient-level trial data related to motor milestone achievement were considered to improve extrapolation predictions in the CEA analysis framework. The other outcomes explored included age at baseline, raw PDMS-2 score, and the expressive communication, receptive communication and cognitive components of the Bayley-III score.

Higher PDMS-2 scores are associated with higher levels of motor milestone achievement following treatment with eladocagene exuparvovec. As shown in Figure 59 to Figure 61 in Appendix J and in Simons *et al.* (2020),[119] whilst high correlation was found between the Bayley-III components and PDMS-2, including Bayley-III in the motor milestone achievement predictions provided counterintuitive results and increased uncertainty in the predictions. Increasing Bayley-III scores resulted in lower likelihood of motor milestone achievement in the growth models, which contradicted the clinical data and clinical expert opinion. The counterintuitive results were likely because Bayley-III was only measured in 2 of the 3 trials, meaning there were problems fitting the limited data to the models. When evaluating the fit of the growth models to the clinical trial data, the best fitting models did not have a relationship with the age of the patient at baseline and age was therefore removed from the final growth model specification. The growth model therefore used PDMS-2 only to estimate motor milestone achievement.

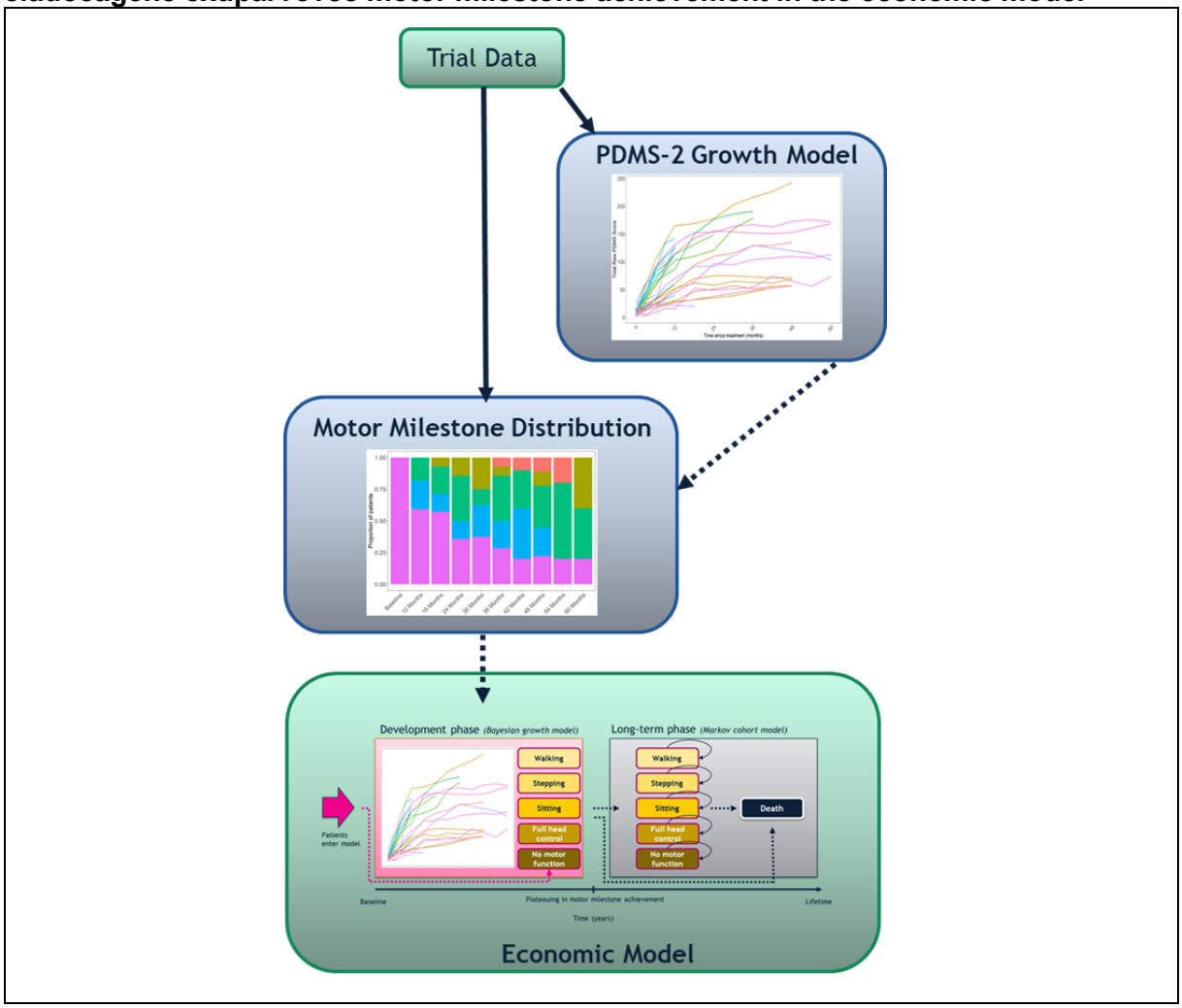
As discussed in Section B.3.2.2.7, PDMS-2 is an appropriate outcome to use to predict motor milestone achievement in the growth model. PDMS-2 is a comprehensive assessment of

motor function and is able to capture slight differences in motor development over time. As discussed in Section B.2, motor milestone achievement was the primary outcome in the trials for eladocagene exuparvovec, as determined based on the attainment of specific items within the PDMS-2 questionnaire. PDMS-2 is clinically relevant as a measure for motor development in patients with AADC deficiency and is also used in CP[49,103,120] (the closest disease proxy to AADC deficiency). It is also mentioned in the NICE guidelines for the diagnosis and management of patients with CP,[102] highlighting its applicability as an outcome to predict motor milestone attainment.

Eladocagene exuparvovec clinical data indicate that patients' improvement in motor milestones may eventually plateau (Section B.2.6). Based on a review of the data, clinical experts also confirmed that a plateauing effect is observed (Clinical Advisory Board 1, February 2020).[26] To capture the plateauing effect and the heterogeneity in motor milestone achievement, growth models were fitted to clinical trial PDMS-2 data. These models aim to estimate motor milestone achievement beyond clinical trial follow-up.

Figure 41 shows how data from the clinical trials were used to estimate eladocagene exuparvovec motor milestone achievement in the economic model.

Figure 41: Schematic showing the process of using trial data to estimate of eladocagene exuparvovec motor milestone achievement in the economic model



Solid arrows indicate estimation of models and dashed arrows represent where estimated fitted values from models are used.

B.3.3.1.1.2. Using Bayesian and cumulative ordered logit modelling to predict motor milestones

Given the limited sample size and heterogeneity in outcomes, motor milestone achievement in the CEA is estimated from clinical trial PDMS-2 scores using Bayesian growth and cumulative ordered logit modelling. The incorporation of motor milestones into the CEA has two stages. Firstly, a patient's PDMS-2 component scores were predicted from clinical trial data through a Bayesian growth model. Following this, cumulative ordered logit models were used to predicted motor milestone achievement based on the predicted PDMS-2 scores. The approach has been extensively validated with HEOR experts during the development of the model.[53,121] Both the Bayesian and the cumulative ordered logit models showed good validation on the available data.

The Bayesian growth model has the advantage of being able to easily present inferences that fully consider uncertainty about unknown quantities, including between-patient heterogeneity Unlike the patient-level simulation approach that can be considered to account for patient heterogeneity (Section B.3.2.2.3), the Bayesian approach does not add unnecessary computational burden in the modelling of outcomes. In addition, the Bayesian growth model uses random effects instead of fixed effect models, as random effects models take into consideration the observed heterogeneity between patients. While the random effects approach makes sense from a methodological point of view, it should be noted that the random effects assumption has placed a large burden on the limited available data. This has led to non-convergence of some model specifications along with the random effects parameters having large credible intervals.

All analyses are limited by the lack of data available. From the 28 patients that received eladocagene exuparvovec in clinical trials, follow-up was a maximum of nine years. While this volume of data is limited, it is expected due to the ultra-rare nature of AADC deficiency. The lack of data is especially pertinent when incorporating components of the Bayley-III score into the model, as only two of the included trials (AADC-010 and AADC-011) collected information on Bayley-III. This would further reduce the sample size and is why Bayley-III was not included in the modelling.

The following models are used in the base-case and scenario analysis:

PDMS-2:

- **Base-case:** Gompertz model with age not impacting any parameters
- **Scenario Analysis:** Asymptotic model with age not impacting any parameters (details of the analysis are described in Appendix J).

Motor milestone achievement:

- **Base-case:** Cumulative ordered logit model with PDMS-2 as a covariate.

B.3.3.1.1.3. Justification for using a Gompertz model to predict PDMS-2 scores in the Bayesian growth model

As discussed above, prediction of motor development through PDMS-2 scores is required to estimate long-term development of AADC deficiency patients following treatment with eladocagene exuparvovec. The growth model estimates patients PDMS-2 score at timepoints using a Bayesian approach (i.e. prior beliefs about the pooled effect is combined with the information from the patients to obtain the posterior distribution of the pooled effect from the patients). The model fitted separate curves to the PDMS-2 score of each patient. It is assumed that patients' progression towards achieving developmental milestones will eventually plateau.

The heterogeneity across patients in improvements in PDMS-2 indicate a mixed-effects model was appropriate. Bayesian regression models approaching an asymptote were fitted using all

available data (using maximum follow-up of 9 years) namely asymptotic, logistic and Gompertz models. These models include mixed-effects that allow for different patients to have different trajectories for their scores. Fixed effects models were considered in the initial analysis, however as they gave a much poorer fit to the data it was decided to proceed with mixed-effects.

The goodness-of-fit statistics were evaluated for the growth models fitted to the AADC deficiency trial data for the N=28 population of patients treated with eladocagene exuparvovec. Results demonstrated that the logistic model was the worst fitting model, with non-convergence when all parameters in the growth model are dependent on age. The two best fitting models were the asymptotic model (fitted with age not impacting on any coefficients) and the Gompertz model (where age does not impact on any of the coefficients).

Internal validation for the Gompertz and asymptote models is presented in Figure 63 in Appendix J. The figure shows that both models fit the observed PDMS-2 trial data well where there are data available up to five years post treatment. For most of the patients with shorter-term follow-up data, the asymptotic model predicted higher PDMS-2 scores than the Gompertz model

Figure 64 in Appendix J presents the results of the two best fitting models (asymptote and Gompertz) for predicting PDMS-2 scores extrapolated to 10 years post-therapy. The figure shows that, despite considerably less than 10 years of follow-up data for some patients, the asymptote and Gompertz growth models generate similar predictions at 10 years post-therapy for those patients with longer-term data. As was the case for the 5-year internal validation data (Figure 63 in Appendix J), for those patients with limited follow-up data, in most cases, the asymptotic model predicted higher PDMS-2 scores than the Gompertz model.

Given the similarities in the motor milestone predictions between asymptote and Gompertz, both approaches would be suitable for the model. However, due to the smaller DIC indicating a statistically better fit, the Gompertz model is used as the base-case and the asymptotic model is used as a scenario analysis for modelling PDMS-2 in the CEA.

B.3.3.1.1.4. Justification for cumulative ordered logit modelling to estimate motor milestone achievement

The second stage of the model predicts a patient's motor milestones at a given time point based on the predicted PDMS-2 scores from the Bayesian modelling stage. A cumulative ordered logit model, a type of cumulative ordered link model, was used to predict the probability of a patient reaching a given milestone at a specified time point based upon their estimated PDMS-2 score at this time. PDMS-2 was the only covariate included in the cumulative ordered logit modelling as it was found to be a significant predictor of motor milestone achievement. As discussed in Section B.3.3.1 age at baseline and Bayley-III were not included as covariates as they either increased the uncertainty in the results or led to a smaller sample size informing the models.

Appendix J presents the median and 95% credible interval from the posterior distributions of the cumulative ordered logit models used to predict a patient's motor milestone achievement. A coefficient of 0.059 indicates greater motor milestone achievement as PDMS-2 scores increase. The goodness-of-fit statistics and validation graphs show that models that only include PDMS-2 as a covariate fit the data well (Figure 65 in Appendix J).

As with selecting the optimal approach to Bayesian modelling step (to predict achievement of PDMS-2), the optimal cumulative ordered logit model was chosen based on the validation graphs, the removal of the Bayley-III components due to counterintuitive results, and after discussion with clinical experts on the validity of the predictions and their extrapolations. Full details of motor milestone prediction in the eladocagene exuparvovec arm of the model is outlined in Appendix J. The predicted distribution of patients across the motor milestone health states based on cumulative ordered logit modelling is presented in Table 41.

Table 41: Distribution of patients across motor milestone health states in the eladocagene exuparvovec cohort (n=28)

	Patient age	No-motor milestone	Full-head alignment	Sitting unassisted	Standing with support	Walking with assistance
Baseline	4	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 1	5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 2	6	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 3	7	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 4	8	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 5	9	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 6	10	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 7	11	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 8	12	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 9	13	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 10	14	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 11	15	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Year 12+	16+	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

B.3.3.1.2. BSC arm

Unfortunately, the prognosis of severe AADC deficiency patients managed with BSC is very poor. Published natural history data demonstrate that over 95% of patients will fail to achieve a motor milestone during their lifetime, and most patients will die in the first decade of life.[8] This is confirmed by clinical experts in the UK.[5]

Eladocagene exuparvovec has only been evaluated in single-arm trials (see Section B.2.6) and there are no clinical trials related to BSC treatments. To inform clinical outcomes for the BSC arm in the CEA, a NHDB was compiled based on all published cases of patients with severe AADC deficiency (Section B.2.9.1).

The use of a natural history comparator is a viable approach in the CEA. Natural history controls are considered appropriate by NICE (2022)[23] when there is an absence of comparator clinical trial data, and were used and accepted by NICE in previous appraisals (e.g., elosulfase

alfa [HST 2][95] and atidarsagene autotemcel [ID1666][99]). Furthermore, UK clinicians[5] and HEOR experts (Economic Advisory Board 1, March 2021)[54] confirmed the appropriateness of using an NHDB for estimating BSC outcomes in this CEA given the lack of trial data. Details of how the NHDB was compiled and analysed are presented in Section B.2.9.

The NHDB provides an opportunity to explore motor milestone achievement in AADC deficiency patients who have a similar profile as those in the clinical trials for eladocagene exuparvovec. In the NHDB, it was found that only 49 patients presented a similar phenotype (i.e. having attained no or poor head control by the age of two) to the trial population and hence were considered in the analysis. In these 49 severe patients, only two experienced some motor development, with one patient achieving the walking with assistance state and one patient being able to roll from side to side (Table 42), highlighting the severe and debilitating nature of AADC deficiency. This aligns with the findings from Hwu *et al.* (2017) natural history study, which shows that just 2% of patients achieve any motor milestones.[6]

The CEA therefore assumes that a small proportion of patients in the BSC arm achieve motor milestone improvements by year five, after which motor milestones remain fixed. The 5-year timeframe is due to the limited follow-up data beyond that timepoint in the NHDB and the limited data overall. The CEA assumes that if a patient in the NHDB jumped more than one motor milestone between observations, the improvement was linear over time. The motor milestone achievement demonstrated in the NHDB is presented in Table 42 and is used for the health state distribution for the BSC arm in the CEA.

Table 42: Distribution of patients across motor milestone health states in the BSC arm of the CEA (based on data from 49 patients in the NHDB)

	Patient age	No-motor function	Full-head alignment	Sitting unassisted	Standing with support	Walking with assistance
Baseline	4	100.00%	0.00%	0.00%	0.00%	0.00%
Year 1	5	97.96%	0.00%	2.04%	0.00%	0.00%
Year 2	6	95.92%	2.04%	0.00%	0.00%	2.04%
Year 3	7	95.92%	0.00%	2.04%	0.00%	2.04%
Year 4	8	95.92%	0.00%	2.04%	0.00%	2.04%
Year 5+	9+	95.92%	0.00%	2.04%	0.00%	2.04%

BSC – best supportive care; CEA – cost-effectiveness analysis; NHDB – Natural History Database

B.3.3.2 Survival

B.3.3.2.1. Limitations in available survival data in AADC deficiency

AADC deficiency is extremely rare and there is therefore limited published survival data. As stated in Section B.1.3.5, from the available published data, it is clear that severe AADC deficiency is associated with premature mortality. Most studies reporting survival data show that patients with severe AADC deficiency patients suffer premature mortality and die in the first decade of life.[1,2,35] For example, Hwu *et al.* (2012) report a mean life expectancy of 4.6 years (based on N=10 survey respondents from patient groups)[35] and Pearson *et al.* (2020) report a mean age of death of 9 years among five of the 63 patients who died by the time of

data analysis.[7] The cause of death in patients with AADC deficiency is related to their comorbidities[35], including motor dysfunction[52], multiple organ failure[35], pneumonia,[7,44] acute complications during an OGC episode,[7] and asphyxia.[44]

In addition to the limited published data, there have been very few deaths in clinical trials for eladocagene exuparvovec, meaning it is not possible to estimate survival based on the clinical trial data. Of the 28 patients treated with eladocagene, only [redacted] had died at the time of the pooled safety data analysis and none were treatment related. See Section B.2.10.7 for further details regarding the reported deaths within the three clinical trials.

In the absence of direct mortality data in patients with AADC deficiency, it has been necessary to model survival in this CEA using alternative approaches.

B.3.3.2.2. Survival based on motor milestones in proxy diseases

Given that patients typically die due to a comorbidity of AADC deficiency, and that the risk of comorbidities/symptoms is expected to vary by motor milestone state (i.e. global symptom improvement), patients in different motor milestone health states are expected to have different survival probabilities. Therefore, mortality of patients in this CEA is determined by their motor milestone health state.

In the absence of survival data from clinical trials for eladocagene exuparvovec and from AADC deficiency in general, a pragmatic literature review was conducted to identify proxy diseases to estimate long-term survival in AADC deficiency.[122] The pragmatic literature review identified CP and SMA type I as the best proxies because they provide survival estimates by motor milestone health state. “True” or “classical” CP (i.e. not having seizures) was identified as the most suitable proxy to estimate AADC deficiency motor milestone-related survival following consultation with global clinical experts at an advisory board (Clinical Advisory Board 1, February 2020[26]), UK clinical experts during validation of this NICE submission (April 2022)[5], and a clinician survey.[25] SMA was not considered appropriate by global and UK clinical experts as, unlike AADC deficiency, it is a neurodegenerative disease.[265] This CEA therefore uses CP motor milestone survival estimates mapped to AADC deficiency motor milestone health states.

B.3.3.2.3. AADC deficiency survival estimates using CP as a proxy

In the CEA, survival is modelled based on patient motor milestone state and not the treatment received. The differential effect on survival of eladocagene exuparvovec vs BSC is driven by differential motor milestone achievement following each treatment. This is consistent with the approach to model survival, which has been accepted in previous NICE HST appraisals (onasemnogene abearvovec, HST15)[97].

As described above, CP motor milestone survival data has been mapped to AADC deficiency motor milestones to generate AADC deficiency survival estimates. The CP proxy data used to inform AADC deficiency survival is based on a study carried out by Brooks *et al. (*2014),[92] who presented survival probabilities in 16,440 CP patients aged four years, followed up from

January 1983 to December 2010. This study has been selected because of its large sample size and its use to model mortality in a cost-effectiveness model for a 2018 NICE guideline on the management of abnormal muscle tone (dystonia). The NICE guideline authors concluded that Brooks *et al.* (2014) provided "up-to-date" survival estimates and that the Californian population was generalisable to England and Wales, highlighting the robustness of the data.

In Brooks *et al.* (2014), CP patients aged 4 years were grouped into the following categories of motor disability: head-lifting in the prone position, rolling, sitting, crawling, and walking. Within each motor health state, patients were further subcategorised by ability to feed. From this information, the authors constructed Kaplan-Meier (KM) survival curves, observing that children with higher motor function who could feed themselves had significantly improved survival than children with lower motor function and who were tube-fed. Survival probabilities of CP patients aged 4 years from Brooks *et al.* (2014) are presented in Table 43.

Based on data from Brooks *et al.* (2014)[92] and clinician input, CP motor milestones were mapped to motor milestones in patients with AADC deficiency as follows:

- **No motor function in AADC deficiency:** Assumed to be equivalent to CP patients who were tube-fed and who did not lift their heads when in the prone position.
- **Full head control in AADC deficiency:** Assumed to be equivalent to CP patients who were able to "lift head but not the chest in the prone position".
- **Sitting unassisted in AADC deficiency:** Assumed to be equivalent to CP patients classified as being able to "lift head and chest, partial rolling".
- **Standing with support in AADC deficiency:** Assumed to be equivalent to CP patients classified as being able to "roll head fully but unable to walk unaided" corresponded to the "standing with support" health state in the model.
- **Walking with assistance in AADC deficiency:** Assumed to be equivalent to CP patients classified as being able to "walk unaided".

It was observed in Brooks *et al.* (2014)[92] that feeding ability also had an impact on survival of patients. Therefore, a weighted average of survival probability based on different levels of feeding ability was determined for each AADC deficiency motor milestone state in the CEA.

As patients included Brooks *et al.* (2014)[92] study were aged four years, survival probability for AADC deficiency patients aged between 0-4 years in the CEA was assumed to be 100%. This was considered an appropriate assumption as the mean baseline age in the CEA for eladocagene exuparvovec was four years old, based on the mean age at baseline in the clinical studies. Table 43 presents the probability of survival for CP patients in each motor milestone health state.

Once the survival probabilities for CP motor milestones were mapped to AADC deficiency motor milestone health states, the survival data were extrapolated for the CEA time horizon. Data from the observed CP population in Brooks *et al.* (2014)[92] were only presented at five ages (4, 15, 30, 45 and 60) for each motor milestone state, which presented some data

limitations. Survival data were therefore extrapolated using parametric curves fitted to each motor milestone state. The Gompertz, Weibull, log normal, log logistic, gamma, and exponential models were fitted to survival data for each motor milestone health state, based on information in NICE DSU 14.[123(p14)]

To determine the most appropriate parametric survival curves to use in the CEA, goodness-of-fit was statistically assessed via Akaike information criterion (AIC) and Bayesian information criterion (BIC) and were subsequently validated by visual inspection. Based on the crossing of curves for different motor milestone health states, selecting survival curves based only on individual AIC and BIC values for each motor milestone health state was not plausible or optimal for this CEA. The CEA therefore considered the best statistical fitting curve across *all* motor milestone health states. While the log-logistic curve had the best overall statistical fit across all milestones (with AIC and BIC values of -221.96 and -222.77, respectively), it resulted in crossing of curves for the "walking with assistance" and "standing with support" curves. The exponential curve was therefore selected for the "walking with assistance" health state as it was the next-best-fitting curve that did not cross with the other motor milestone health state curves. Scenario analyses (Section B.3.7.1) explore the use of different parametric curves to extrapolate the Brooks *et al.* (2014)[92] data.[92]

Following the fit of the parametric survival curves, survival was adjusted for background mortality based on England and Wales general population mortality from the Office for National Statistics.[124] Survival curves and landmark estimates for each AADC deficiency motor milestone health state are shown in Figure 42 and Table 44. In addition to statistical fit, curves were assessed for visual fit and clinical plausibility. The log-logistic and exponential curves appeared to fit the data well based on visual inspection. UK clinical experts[5] commented that the motor milestone health state survival estimates derived from Brooks *et al.* (2014)[92] were slightly longer for all motor milestones than may be expected in AADC deficiency patients; however, as survival is dependent on motor milestone achieved and not treatment received, the same survival estimates are applied for both eladocagene exuparvovec and BSC within each motor milestone health state.

Table 43: Probability of survival among patients with CP aged 4 years - Brooks *et al.* (2014)[92]

Age (years)	Does not lift head in the prone position			Lifts head but not chest in the prone position			Lifts head and chest, partial rolling			Full rolling does not walk unaided			Walks unaided		
	Tube-fed (n=482)	Fed orally by others (n=615)	Self-fed (n=50)	Tube-fed (n=303)	Fed orally by others (n=795)	Self-fed (n=103)	Tube-fed (n=265)	Fed orally by others (n=962)	Self-fed (n=329)	Tube-fed (n=475)	Fed orally by others (n=1,643)	Self-fed (n=4,906)	Tube-fed (n=125)	Fed orally by others (n=188)	Self-fed (n=5,199)
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10	0.75	0.85	0.97	0.79	0.89	0.97	0.82	0.93	0.97	0.9	0.96	0.99	0.96	0.97	1
15	0.58	0.73	0.9	0.66	0.8	0.92	0.71	0.86	0.95	0.85	0.93	0.98	0.94	0.97	0.99
20	0.41	0.56	0.9	0.55	0.67	0.86	0.65	0.78	0.92	0.77	0.88	0.96	0.86	0.97	0.98
25	0.31	0.47	-	0.44	0.54	0.76	0.54	0.66	0.87	0.64	0.84	0.94	0.81	0.97	0.96
30	0.26	0.43	-	0.34	0.48	0.76	0.4	0.55	0.77	0.56	0.77	0.92	-	0.87	0.94

Abbreviations: CP – cerebral palsy

Table 44: Landmark estimates of AADC deficiency survival based on motor milestone state, adjusted for background mortality

	Year of follow-up in the CEA*															
	0	**1**	**2**	**3**	**4**	**5**	**10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
No-motor function	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Full-head control	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Sitting unassisted	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Standing with support	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Walking with assistance	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

**Patients enter the CEA aged 4 years of age (based on the age at baseline in the eladocagene exuparvovec studies). Survival is assumed to be 100% up to the age of 4 years.*
Abbreviations: AADC – aromatic L-amino acid decarboxylase; CEA – cost-effectiveness analysis

Figure 42: Base-case survival by AADC deficiency motor milestone health state, adjusted for background mortality

Abbreviations: AADC – aromatic L-amino acid decarboxylase

B.3.4. Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

No HRQoL (including EQ-5D) data were collected for patients with AADC deficiency within the AADC-010, AADC-011, and AADC-CU/1601 clinical trials for eladocagene exuparvovec. Furthermore, clinical experts have highlighted that EQ-5D is not sensitive enough to capture cognitive limitations associated with AADC deficiency.[26]

In the absence of HRQoL data from the clinical trials for eladocagene exuparvovec, a vignette study was conducted using UK general population TTO to elicit utility outcomes for the five motor milestone health states in the model. This methodology is consistent with the hierarchy of preferred HRQoL methods as stated in the NICE health technology evaluations manual (2022)[23] and NICE DSU technical support document 11, when EQ-5D is not appropriate.[111]

B.3.4.2 Mapping

No mapping has been conducted as HRQoL data were not collected in clinical trials for eladocagene exuparvovec.

B.3.4.3 Health-related quality-of-life studies

An SLR was undertaken to identify previous HRQoL data and studies relevant to the decision problem. The methods, search strategies and inclusion and exclusion criteria used, along with results for the SLR of HRQoL studies are presented in (Appendix H: Health-related quality-of-life studies).

Of the 61 full text publications assessed at the 2nd pass of the SLR, 21 publications were applicable for HRQoL evaluation. Of the 21 publications assessed, only 6 publications meeting the selection criteria of the HRQoL review question were extracted. Furthermore, one publications was identified for HRQOL data in a grey literature search. Overall, seven publications evaluated quantitative HRQoL data. A summary of the publications extracted for quantitative HRQoL are presented in (Appendix H: Health-related quality-of-life studies).

As no HRQoL data were collected in the eladocagene exuparvovec clinical trials, it was not possible to conduct a comparison between the values derived from the literature and those reported in the clinical trials.

B.3.4.4 Adverse reactions

Full details regarding adverse event data in trials for eladocagene exuparvovec can be found in Section 115B.2.10.

As is standard practice in CEAs, the CEA considers moderate-to-severe TEAEs as they are assumed to incur healthcare resource use, costs, and an impact on HRQoL. Moderate-to-severe TEAEs occurring in over 20% of patients up to Month 12 following eladocagene exuparvovec were considered in the CEA. In trials with eladocagene exuparvovec, [redacted]% of the 28 patients treated with eladocagene exuparvovec experienced a moderate to severe TEAE up to Month 12 following gene-replacement therapy. Moderate-to-severe TEAEs affecting over 20% of patients included dyskinesia ([redacted]% moderate, [redacted]% severe), pneumonia ([redacted]% moderate, [redacted]% severe), gastrointestinal disorders ([redacted]% moderate, [redacted]% severe) and gastroenteritis ([redacted]% moderate, [redacted]% severe). [20]

Moderate to severe TEAEs in the CEA are applied to the eladocagene exuparvovec arm only as similar information is not available for patients in the BSC arm. The CEA conservatively therefore assumes that TEAEs with BSC are captured in the disease management costs. This is a conservative approach as it does not consider TEAE-related disutilities with BSC.

The annual rate of adverse events in the CEA for patients receiving eladocagene exuparvovec and BSC are presented in Table 45.

Table 45: Moderate-to-severe TEAEs occurring in ≥20% patients at 12 months post-gene-replacement therapy across the three pivotal trials (N=28)

Adverse event	Eladocagene exuparvovec		BSC*	
	Moderate	Severe	Moderate	Severe
Dyskinesia	[redacted]%	[redacted]%	0%	0%

Pneumonia	[redacted]%	[redacted]%	0%	0%
Gastrointestinal disorders	[redacted]%	[redacted]%	0%	0%
Gastroenteritis	[redacted]%	[redacted]%	0%	0%

TEAEs occurring in the trials were coded per the MedDRA coding dictionary version 19.1; Severity of adverse events was determined by the investigator.
**BSC TEAEs were conservatively assumed to be captured as part of the disease management costs.*
BSC – best supportive care; TEAE – treatment emergent adverse event
Source: Integrated summary of safety data tables[20]

B.3.4.4.1. TEAE disutilities

TEAE-related disutilities are included in the base-case CEA. As the CEA only considers TEAEs associated with eladocagene exuparvovec (because comparable BSC data were not available), TEAE disutilities are only considered for patients receiving eladocagene exuparvovec. TEAE disutility values were identified through a targeted literature review. All values were derived from Table 3 the supplementary papers in Sullivan *et al*. (2011), which reported a catalogue of UK-based EQ-5D values for a range of health conditions.[125] In the absence of evidence on duration of TEAEs, it was conservatively assumed that symptoms of TEAEs lasted for up to 60 days. Disutility values are presented in Table 46.

Table 46: TEAE disutility values used in the CEA

		Description in Sullivan *et al.* (2011)	
Dyskinesia	0.0669	Assumed equal to epilepsy, convulsions	60
Pneumonia	0.0336	Assumed equal to asthma	60
Gastrointestinal disorders	00512	Assumed equal to “other gastrointestinal disorders”	60
Gastroenteritis	0.0725	Assumed equal to non-infectious gastroenteritis	60

Abbreviations: TEAE – treatment-related adverse event
Source: Sullivan et al., 2011[125]

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.5.1. Rationale for TTO-derived motor milestone health state utility values

To overcome the lack of HRQoL and utility data, PTC developed motor milestone health state vignettes (Hanbury *et al.* 2021[56]) aligned with the five motor milestone health states in the CEA, and then elicited utilities using a TTO in the general UK population. Vignettes were based on motor milestone health states aligned to those used in the CEA: no motor function, full head control, sitting unassisted, standing with support, and walking with assistance.[56] The use of vignettes is in line with hierarchy of preferred HRQoL methods published NICE health technology evaluations manual (2022),[23] which states that vignettes may be appropriate when EQ-5D data are not available.

The vignettes were then used to elicit health state utility values via various methods (TTO, SG, and DCE), which were each published by Smith *et al.* and identified as part of the SLR for this submission. The utility elicitation publications relevant to this submission are as follows:

UK time-trade off and standard gamble: Smith *et al.* J Patient Rep Outcomes 2021;5(1):130. doi: 10.1186/s41687-021-00403-0.[27]

UK discrete choice experiment: Smith *et al.* Patient Relat Outcome Meas 2021; 12: 97-106. doi: 10.2147/PROM.S294628. eCollection.[126]

For the base-case CEA, utility values were elicited from the TTO study by Smith *et al.* (2021).[27] The TTO study was selected over the SG and DCE studies for the base-case analysis as TTO is more rigorous and has repeatedly been shown to be easier to understand and complete,[23] with respondents in this UK TTO having less difficulty distinguishing between the poorest health states than for the SG.[27] TTO is preferred over SG or DCE in the NICE health technology evaluations manual (2022)[23] and the NICE DSU technical support document 11,[111] when EQ-5D is not appropriate.

B.3.4.5.2. Elicitation of motor milestone health state values using TTO

In the base-case analysis of this CEA, a UK TTO was conducted to derive utility values from five motor milestone health state vignettes. The five motor milestone health state vignettes associated with AADC deficiency were developed as part of the study by Hanbury *et al.* (2021)[56], and were classified as follows: no motor function, full head control, sitting unsupported, standing with support, walking with assistance.[56] Vignettes were defined from a parent/caregiver perspective and were informed by a pragmatic literature search, a review of case reports, and advisory boards with clinical experts and caregivers of AADC deficiency patients. Each motor milestone health state vignette described symptoms associated with AADC deficiency (hypotonia, OGC, motor impairment, dystonia, feeding and swallowing difficulties, mental impairment, irritability, sleep, and autonomic dysfunction.[56] In line with the clinical trial data suggesting global symptom improvement, symptoms were described as less severe in the less severe motor milestones vignettes.[56]

To develop the vignettes, a pragmatic literature review was conducted along with discussions with three parent/caregivers from the USA. The discussions focused on the challenges and obstacles associated with caring for a person with AADC deficiency. It was considered more feasible, robust, and reliable to discuss vignettes with parents/carers than the children with AADC deficiency themselves given the severity of the condition. Following caregiver discussions, a “symptom matrix” was developed to summarise AADC deficiency symptoms and their severity, and this matrix informed the development of motor milestone health state vignettes. Symptoms were given across the five motor milestone states and included motor impairment, hypotonia, oculogyric crisis, dystonia, feeding and swallowing difficulties, weight, mental impairment, irritability/screaming child, sleep and autonomic. Symptoms in the five motor milestone health state vignettes improve globally with improving motor function (i.e. “no-motor function” is associated with the worst global symptoms and “walking with assistance” is

associated with the best), in line with the literature and expert validations indicating that there is global symptom improvement as motor function improves.[59]

The symptom matrix and vignettes were reviewed and validated by three caregivers. They were also reviewed and validated by three clinicians (including a UK clinician) as part of the vignette study, and by international clinicians in an advisory board (clinical advisory board 1, February 2020).[26] The final clinician- and caregiver-validated vignettes were used in the UK TTO study.

The five validated motor milestone health state vignettes were then used to elicit utility values through a TTO study involving 1,598 UK adults of the general population (i.e. not parents or caregivers of children with severe/life-threatening conditions).[27] The participants were asked to imagine themselves as a parent or caregiver of the child described in each of the five motor milestone health state vignettes.[27] Participants were asked to indicate how much of the child's life they were willing to trade-off for the child to live the remaining years in full health.[27] A total of 1,598 participants completed the online survey, of which 1,039 provided congruent responses that were then used in the TTO study (incongruent responses were defined as rating the "worst" health state ("bedridden") higher than the "best" health state ("able to walk") on the TTO task).[27]

The TTO time-period for each vignette was ten years. This is the most commonly applied time-horizon for TTO tasks.[127] Ten years was considered appropriate for this TTO as severe AADC deficiency patients typically remain in the "no motor function" state for their lifetime and usually die before adulthood.

The overall health states utilities derived from the UK TTO study are presented in Table 47. These utilities are used in the base-case for the CEA. The motor milestone HSUV derived from the UK TTO study were chosen for the base-case CEA as they show that utilities improve across the motor milestone states. The UK TTO values were also lower and more conservative than utility values derived from the SG and DCE studies. Scenario analysis in Section B.3.7.1 explore the CEA with different utility elicitation methods.

Table 47: Motor milestone state utility values from the UK TTO study

Motor milestone health state	TTO utility values
No-motor function	0.494
Full-head control	0.537
Sitting unassisted	0.631
Standing with support	0.676
Walking with assistance	0.728

Abbreviations: TTO - time-trade off; UK = United Kingdom
Source: Smith et al., 2021[27]

B.3.4.5.3. Caregiver HRQoL

AADC deficiency has a major physical, emotional and financial impact on families and carers of the patient.[61] Caring for a child with AADC deficiency requires around the clock, one-to-one support with all aspects of daily living[13] and has a severe impact on a caregiver's quality-of-

life. Due to devastating nature of AADC deficiency to patients and associated caregiver burden, it is essential to consider caregiver QoL in the base case CEA in this NICE appraisal and is consistent with the NICE manual for health technology evaluations (2022).[23]

Quantitative caregiver QoL data were not collected in clinical trials for eladocagene exuparvovec or identified in AADC deficiency patients in the SLR. Therefore, a review of NICE HSTs was conducted to identify caregiver disutility values based on motor function that could be applied to AADC deficiency. The review focused on caregiver quality-of-life data that were deemed acceptable to NICE.

The most appropriate disutility values for this AADC deficiency CEA were for the disutility values accepted by NICE in the submission for elosulfase alfa for the treatment of mucopolysaccharidosis type IVA (HST 2)[95], which used UK caregiver EQ-5D disutility values derived from observational studies in multiple sclerosis (MS) by Acaster *et al.* (2013)[28] and Gani *et al.* (2008)[128]. While not using the same proxy disease as for other outcomes in the CEA (e.g. CP for survival), the MS caregiver disutility values were considered appropriate for AADC deficiency as they provide disutility values for motor milestone health states, and the severity of MS motor milestones aligns with those for AADC deficiency. Appropriate caregiver disutility values were not identified in the two closest proxy conditions: CP or SMA. Furthermore, both the Acaster and Gani studies were conducted with UK caregivers. Based on the precedence, availability, and generalisability of the disutility values, the Acaster and Gani studies were the most appropriate data sources for modelling caregiver disutility.

To derive disutility values for this CEA, the MS motor milestone severity levels were mapped to AADC deficiency motor milestone health states:

- "No-motor function" and "full-head control" AADC deficiency motor milestone health states were assumed to correspond to the MS "bedridden" state.
- The "sitting unassisted" and "standing with support" health states were mapped to the MS wheelchair/scooter state.
- No caregiver disutility values are assumed for the "walking with assistance" state.

The AADC deficiency motor milestone health state disutility values mapped from Acaster *et al.* (2013)[28] are reported in Table 48.

Table 48: Caregiver disutility values

AADC deficiency motor milestone state	Base case: Acaster *et al.* (2013)
No-motor function	0.09
Full-head control	0.09
Sitting unassisted	0.03
Standing with support	0.03
Walking with assistance	0.00

Caregiver disutility values in AADC deficiency were mapped from published values for caregivers of MS patients (Acaster et al. (2013))
Abbreviations: AADC – aromatic L-amino decarboxylase

In the absence of data on the mean number of caregivers required to support patients with AADC deficiency, a pragmatic literature search of similar NICE appraisals was conducted to identify proxy data. In the NICE appraisal for risdiplam (TA755), 2.2 caregivers per patient was considered acceptable by NICE.[129] Given the similarities in terms of symptoms related to physical disability and mobility issues, these SMA proxy data were identified as the closest AADC deficiency proxy with relevant caregiver data considered acceptable to NICE. The base case CEA for this AADC deficiency submission therefore assumes 2.2 caregivers for patients with no-motor function (the most severe), reflecting the high burden of caregiving for a patient with the most severe symptoms in AADC deficiency (Table 49).

The CEA assumes that patients with worse motor function will require more caregiver support than those with greater motor function. This assumption has been validated with a UK clinical expert who agreed that the caregiver burden of AADC deficiency would improve as motor function improves.[5] The CEA assumes that, as motor function improves, the number of caregivers decreases in a linear fashion from 2.2 caregivers (no-motor function) to 1.2 caregivers ("walking with assistance"). This approach to use differing caregiver numbers for different health states is in line with that used for nusinersen in SMA (3 caregivers in the worst health state, 2 in the best health state)[98] and is consistent with committee discussions for ataluren in Duchenne Muscular Dystrophy, which stated that "the need for support increases substantially after the person loses their ability to walk".[94] UK clinicians consulted as part of this AADC deficiency appraisal confirmed that 2.2 caregivers is appropriate for patients with no motor function and stated that AADC deficiency patients with more severe symptoms would require more care than those with less severe symptoms.[5]

Table 49: Number of primary caregivers associated with each motor milestone state

AADC deficiency motor milestone health state	Number of primary caregivers
No-motor function	2.2
Full-head control	1.9
Sitting unassisted	1.6
Standing with support	1.3
Walking with assistance	1.2

Based on UK clinician input[5] and TA755 for treatment with for risdiplam in SMA[129]
Abbreviations: AADC – aromatic L-amino decarboxylase; SMA – spinal muscular atrophy; TA – technology appraisal

In addition to caregiver disutilities, a caregiver bereavement disutility value is also included in the CEA. This is in line with the bereavement disutility estimate reported in the NICE appraisal for Strimvelis (HST 7)[93], derived from Song *et al* (2010).[117] The study used multiple approaches to estimate parental couples' disutility of losing a child, with estimated disutility values ranging between 0.04 and 0.03. In this CEA, the average disutility value from Song *et al*. (2010)[117] is applied in the CEA: 0.037. The caregiver disutility value is included in the base case CEA to capture the full extent that caring for a child with AADC deficiency can have on the QoL of a caregiver. Table 50 provides a summary of the QoL values included in the base-case of the CEA.

Table 50: Summary of utility values used in the CEA

State	Mean utility value (standard error)	95% CI	Reference in submission (section and page number)	Justification
Health states utility values				
No-motor function	0.494 (0.3429)	0.4751 to 0.5129	Section B.3.4.5, Page 159	Due to difficulties in collecting HRQoL values from the clinical trials for eladocagene exuparvovec and the very limited literature, motor milestone health state utility values were based on a publication by Smith *et al.* (2021)[27] identified in the SLR. The utilities are derived from a UK TTO study using five motor milestone health state vignettes. Vignettes were validated by clinical experts in an advisory board[26] and by three caregivers.
Full-head control	0.5369 (0.3255)	0.519 to 0.5548		
Sitting unassisted	0.6312 (0.3099)	0.6141 to 0.6482		
Standing with support	0.6755 (0.3073)	0.6755 to 0.6925		
Walking with assistance	0.7279 (0.3052)	0.7111 to 0.7447		
Adverse event rates – eladocagene exuparvovec				
Dyskinesia - Moderate	[redacted]	-	Section B.3.4.4, Page 157	The CEA considers moderate to severe TEAEs occurring in ≥20% of patients within 12 months of eladocagene exuparvovec in clinical studies. Moderate-to-severe TEAEs are assumed to incur healthcare resource use, costs and have the biggest impact on HRQoL. Moderate to severe TEAEs are considered for treatment with eladocagene exuparvovec only as the relevant data were not available for the BSC treatment cohort. The CEA assumes that BSC TEAEs are captured in disease management costs.
Pneumonia - Moderate	[redacted]	-		
Gastrointestinal disorders - Moderate	[redacted]	-		
Gastroenteritis - Moderate	[redacted]	-		
Dyskinesia – Severe	[redacted]	-		
Pneumonia – Severe	[redacted]	-		
Gastrointestinal disorders - Severe	[redacted]	-		
Gastroenteritis - Severe	[redacted]	-		
Adverse events - disutilities				
Dyskinesia	0.067 (0.013)	-	Section B.3.4.4.1, Page 158	The CEA considers TEAE-related disutilities. The TEAE disutility values are based on published literature by Sullivan *et al.* (2011) [125]. The duration of the events was assumed to be (60 days) in the model due to the absence of data from the literature.
Pneumonia	0.034 (0.007)	-		
Gastrointestinal disorders	0.051 (0.010)	-		
Gastroenteritis	0.075 (0.015)	-		
Caregiver disutilities				
No-motor function	0.09 (0.02)	-	Section B.3.4.5.3, Page 160	No QoL data were collected for caregivers within the clinical trials. Caregiver disutility values were therefore derived from caregivers of patients with MS, as reported in Acaster *et al.* (2013)[28]. EQ-5D
Full-head control	0.09 (0.02)	-		
Sitting unassisted	0.03 (0.01)	-		

Standing with support	0.03 (0.01)	-		utility decrements for UK caregivers of MS patients were mapped to the motor milestone states for AADC deficiency and used in the CEA.
Walking with assistance	0.00 (0.00)	-		
Caregiver bereavement disutility	0.037 (0.007)	-	Section B.3.4.5.3, Page 160	Caregiver bereavement is included in the base-case to fully capture the impact of caring for a child with AADC-. The use of a caregiver bereavement disutility aligns with the NICE HST appraisal for Strimvelis (HST 7)[93].

Abbreviations: BSC – best supportive care; CEA – cost-effectiveness analysis; HRQoL - health-related quality-of-life; HST - highly specialised technology; MS – multiple sclerosis; NICE – National Institute of Health and Care Excellence; QoL – quality-of-life; SLR – systematic literature review; TEAE – treatment-emergent adverse events; TTO – time trade-off

B.3.5. Cost and healthcare resource use identification, measurement, and valuation

An SLR was undertaken to identify cost and resource use associated with AADC deficiency. Of the 55 publications identified from the SLR that met the selection criteria, following the first and second pass and were extracted overall, 14 publications evaluated cost and resource use associated with AADC deficiency and its management. Please see Appendix I for more details on the methods, strategy, inclusion/exclusion criteria and results from the SLR.

The publication by Saberian *et al.* (2021)[112] reported health care resource use values associated with disease management, such as follow-ups from a multidisciplinary team, medical procedures and technical procedures, have been utilised in the model. The following sections describe the following costs and resource use utilised in the CEA in further detail:

- For intervention and comparator, including acquisition and administration costs.
- Health state
- Adverse events.

Throughout the CEA, a 2020 cost year was used.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1. Eladocagene exuparvovec

B.3.5.1.1.1. Acquisition costs

Eladocagene exuparvovec has an NHS list price of £[redacted]. In the base-case CEA, a confidential simple patient access scheme (PAS) discount of [redacted] % (to 4 decimal places) is applied to the approved NHS list price. The PAS price for eladocagene exuparvovec is £[redacted]. This is applied in the CEA as a one-off cost given that eladocagene exuparvovec is a gene-replacement therapy that requires one administration that provide sustained, long-term benefits.

B.3.5.1.1.2. Administration and monitoring costs

Prior to administration of eladocagene exuparvovec, patients are assumed to require two MRI scans in addition to the scans that they would receive as part of usual practice. One scan is expected to take place several weeks before administration to determine eligibility and suitability for gene-replacement therapy, and one is expected to take place immediately before the surgery to aid with positioning of the infusion. The CEA uses a cost of £147.34 per MRI scan, based on the 2019/2020 NHS Reference Cost for a weighted average of EMRI scan of one area, without contrast, 18 years and under".

Eladocagene exuparvovec is administered through bilateral intraputaminal infusion during a single surgical session. A relevant NHS Hospital Resource Group (HRG) code does not exist for intraputaminal infusions. The cost of administration is therefore estimated to be £2,450.79,

based on the National Schedule of Reference Costs 2019/2020[8] for “very major and major intracranial procedures among paediatric patients”, which are assumed to be a sufficient proxy of the level of complexity of the intraputaminal injection required for eladocagene exuparvovec. This approach to costing the administration of eladocagene exuparvovec aligns with advice provided by NHS England and NICE during pre-submission meetings. The intraputaminal injection is assumed to be executed in a day case setting, in line with intracranial injections for SMA patients.

Immediately following gene-replacement therapy, patients are conservatively assumed to have a paediatric intensive care stay followed by a paediatric ward, before being discharged. Patients are also conservatively assumed to have 3 CT scans, 2 PET scans, and 1 CSF test for monitoring purposes for complications and/or assess for the functioning AADC enzyme. In addition, patients are conservatively assumed to have up to 8 follow-up visits in addition to usual care in the three months post-surgery. Resource use and costs associated with pre-, peri-, and post-eladocagene exuparvovec administration are provided in Table 51.

Table 51: Pre- and post-administration resource use and costs associated with administration of eladocagene exuparvovec

Resource use	Cost per unit	Frequency	Total cost	Reference
Pre-operative resource use				
MRI scan	£147.34	2	£294.68	National Schedule of Reference Costs 2019/2020: weighted average of MRI scan of one area, without contrast, 18 years and under (RD01B - RD01C)[114]
Post-operative resource use				
Paediatric intensive care unit (per stay)	£3,305.99	1	£3,305.99	National Schedule of Reference Costs 2019/20: Paediatric Critical Care, Advanced Critical Care 3 (XB03Z) [114]
Paediatric ward stay (per stay)	£3,064.90	1	£3,064.90	National Schedule of Reference Costs 2019/20: Paediatric Critical Care, Advanced Critical Care 5 (XB01Z) [114]
Multidisciplinary team follow-up visits post-surgery	£295.64	8	£2,365.12	National Schedule of Reference Costs 2019/20: paediatric neuro-disabilities, non-admitted F2F follow-up visit (WF01A) [114]
CT scan	£32.41	3	£97.23	National Schedule of Reference Costs 2019/2020: CT, Consultant Led (DIM001)[114]
PET scan	£172.94	2	£345.88	National Schedule of Reference Costs 2019/20: Positron Emission Tomography (PET), Consultant Led (DIM010)[114]
Lumbar puncture	£1,225.78	1	£1,225.78	National Schedule of Reference Costs 2019/2020: weighted average of day case cost for diagnostic spinal puncture (HC72B and HC72C)[114]

Abbreviations: CSF – cerebral spinal fluid; CT – computerised tomography; MRI – magnetic resonance imaging; PET – positron emission tomography

B.3.5.1.2. BSC

As detailed in Section B.1.3.8, there are no NICE or NHS guidelines on the clinical management of AADC deficiency in the UK. No disease-modifying treatments are licenced specifically for patients with AADC deficiency, and therefore the comparator in this CEA is BSC. BSC is highly individualised and consists of symptomatic treatments, support from a multidisciplinary team of specialists, and medical and technical procedures.

B.3.5.1.2.1. Symptomatic treatments used as part of BSC

In the absence of UK-specific guidelines, the current management of patients with AADC deficiency (including treatments and treatment regimens) are informed in the CEA using a consensus guideline for the diagnosis and treatment of AADC deficiency by Wassenberg *et al.* (2017)[2]. The main source for the doses of the treatments in the BSC treatment basket is Wassenberg *et al.* (2017)[2], with Brun *et al.* (2010)[15] being used as an additional source.

As there are different drugs within the dopamine agonists and MAO inhibitors group, a different weight is attached to each drug, corresponding with the proportion of patients that are expected to be treated with each drug. Wassenberg *et al.* (2017)[2] states that patients may come off treatment if there is no response, but then may restart treatment if symptoms deteriorate. Therefore, it is assumed, in lieu of other evidence, that patients continue all symptomatic treatments for the time horizon of the model.

Table 52 presents an overview of the dosing regimens and the weights attached for each BSC treatment. Unit costs for BSC treatments are presented in Table 53 and were obtained from the BNF[113] for 2021 costs. All BSC treatments are administered orally and therefore no administration cost have been assumed.

The model assumes that BSC use is dependent on motor milestone achievement (i.e. the proportion of patients using each symptomatic treatment varies by motor milestone health state). For the proportion of patients per treatment arm receiving BSC, see Table 57. Because BSC treatment use in the CEA is based on motor milestone health state, it is assumed that eladocagene exuparvovec patients also receive BSC treatments.

Table 52: Dosing regimens for BSC treatments

Treatment category	Drug	Weight	Dose regimen	Source
Dopamine agonists	Pramipexole	18.2%	0.5 mg / kg / day	Wassenberg (2017)[2]
	Ropinirole	18.2%	24 mg / day	Wassenberg (2017)[2]
	Rotigotine	54.5%	8 mg /day	Wassenberg (2017)[2]
	Bromocriptine	9.1%	0.5 mg / kg / day	Wassenberg (2017)[2]
MAO inhibitors	Tranylcypromine	38.9%	0.5 mg / kg / day	Wassenberg (2017)[2]
	Selegiline	61.1%	0.3 mg / kg / day	Wassenberg (2017)[2]
Vitamin B6	Pyridoxine Hydrochloride	100%	200 mg / day	Wassenberg (2017)[2]
Anticholinergic agents	Trihexyphenidyl hydrochloride	100%	60 mg /day	Wassenberg (2017)[2]
Diazepam	Diazepam	100%	40 mg /day	Wassenberg (2017)[2]
Melatonin	Melatonin	100%	8 mg / day	Wassenberg (2017)[2]
Clonidine	Clonidine	100%	3 mg /day	Wassenberg (2017)[2]
L-Dopa	Levodopa	100%	5 mg / kg /day	Wassenberg (2017)[2]
Folic acid	Folic acid	100%	5 mg / day	Wassenberg (2017)[2]
Dietary supplement	Ensure Plus Advance	100%	220 ml / day	Assumption
Vitamin D	Colecalciferon	100%	400 mg / day	BNF

Abbreviations: BNF – British National Formulary; BSC – best supportive care; MAO - monoamine oxidase

Table 53: BSC treatment acquisition costs

Drug	Units/ pack	Strength (mg/unit)	Cost per package	Cost per unit	Source
Dopamine agonists					
Pramipexole	100	180 mg	£13.92	£0.14	BNF (Oct 2021)[113]
Ropinirole	84	2 mg	£21.51	£0.26	BNF (Oct 2021)[113]
Rotigotine	28	4 mg	£123.60	£4.41	BNF (Oct 2021)[113]
Bromocriptine	100	10 mg	£74.99	£0.75	BNF (Oct 2021)[113]
MAO inhibitors					
Tranylcypromine	28	10 mg	£429.61	£15.34	BNF (Oct 2021)[113]
Selegiline	100	10 mg	£32.23	£0.32	BNF (Oct 2021)[113]
Vitamin B6					
Pyridoxine Hydrochloride	60	10 mg	£0.77	£0.01	BNF (Oct 2021)[113]
Anticholinergic agents					
Trihexyphenidyl hydrochloride	84	2 mg	£5.51	£0.07	BNF (Oct 2021)[113]
Benzodiazepines					
Diazepam	28	10 mg	£1.06	£0.04	BNF (Oct 2021)[113]
Melatonin	30	3 mg	£19.75	£0.66	BNF (Oct 2021)[113]
Clonidine					

Clonidine	100	0.1 mg	£8.04	£0.08	BNF (Oct 2021)[113]
L-Dopa					
Levodopa	30	200 mg	£20.79	£0.69	BNF (Oct 2021)[113]
Folic acid (vitamin B9)					
Folic acid	28	5 mg	£1.03	£0.04	BNF (Oct 2021)[113]
Dietary supplement					
Ensure Plus Advance	220	1 ml	£2.20	£0.01	BNF (Oct 2021)[113]
Vitamin D					
Colecalciferol	30	800 mg	£2.95	£0.10	BNF (Oct 2021)[113]

Abbreviations: BNF - British National Formulary; MAO - monoamine oxidase

B.3.5.1.2.2. Resource use as part of current BSC

The management of patients with AADC deficiency requires a multidisciplinary team of specialists, including gastroenterologist, neurologist, pulmonologist, ear/nose/throat (ENT) doctor, ophthalmologist, endocrinologist, orthopaedic surgeon, geneticist, speech therapist, dietician, and occupational therapist. As with BSC treatment use, the annual number of specialist visits, hospitalisations, and accident and emergency (A&E) attendances varies according to motor milestone health state and can be found in Section B.3.5.2. The approach undertaken is in line with NICE and US Institute for Clinical and Economic Review appraisals for SMA.[98,130] Unit costs are presented in Table 54 and were sourced from the National Schedule of Reference Costs 2019/2020[114] and the PSSRU.[115]

Table 54: Unit costs for visits from a multidisciplinary team, hospitalisations, and A&E attendances

Resource use	Cost	Source
Dietician	£60.00	PSSRU 2020: Band 7 Dietitian cost per hour (page 150)[115]
Endocrinologist	£231.85	National Schedule of Reference Costs 2019/2020: paediatric endocrinology, non-admitted F2F follow-up visit (WF01A)[114]
Gastroenterologist	£219.40	National Schedule of Reference Costs 2019/2020: paediatric gastroenterologist, non-admitted F2F follow-up visit (WF01A)[114]
General practitioner	£39.23	PSSRU 2020: cost of GP consultation lasting 9.22 minutes (with qualification including direct care staff costs)[115]
Geneticist	£371.90	National Schedule of Reference Costs 2019/2020: clinical genetics, non-admitted F2F follow-up visit (WF01A) [114]
Neurologist	£295.64	National Schedule of Reference Costs 2019/2020: paediatric neuro-disabilities, non-admitted F2F follow-up visit (WF01A) [114]
Nurse	£10.50	PSSRU 2020: cost of nurse (at GP practice) lasting 15 mins[115]
Occupational therapy	£141.00	PSSRU 2020: Occupational therapy services for children's health (page 70)[115]
Ophthalmologist	£110.13	National Schedule of Reference Costs 2019/2020: paediatric ENT, non-admitted F2F follow-up visit (WF01A)[114]
Orthopaedic surgeon	£136.91	National Schedule of Reference Costs 2019/2020: paediatric trauma and orthopaedics, non-admitted F2F follow-up visit (WF01A) [115]

Otolaryngologist	£130.63	National Schedule of Reference Costs 2019/2020: paediatric ENT, non-admitted F2F follow-up visit (WF01A) [115]
Paediatrician	£224.27	National Schedule of Reference Costs 2019/2020: paediatrics, non-admitted F2F follow-up visit (WF01A)[115]
Physiotherapist	£48.26	National Schedule of Reference Costs 2019/2020: physiotherapy, non-admitted F2F follow-up visit (WF01A)[115]
Pulmonologist	£218.23	National Schedule of Reference Costs 2019/2020: respiratory medicine, non-admitted F2F follow-up visit (WF01A)[115]
Psychiatrist	£350.55	National Schedule of Reference Costs 2019/2020: child and adolescent psychiatry, non-admitted F2F follow-up visit (WF01A)[115]
Psychologist	£168.76	National Schedule of Reference Costs 2019/2020: psychotherapy, non-admitted F2F follow-up visit (WF01A)[115]
Speech therapist	£60.00	PSSRU 2020: Band 7 Speech therapist cost per hour (p150) [115]
Hospitalisation	£1,212.80	National Schedule of Reference Costs 2019/2020: elective inpatient for special screening, examinations and genetic disorders (WH15Z)[115]
A&E attendance	£205.09	National Schedule of reference costs 2019/2020: weighted average of A&E admission and emergency medicine (VB01Z-VB09Z)[115]

Abbreviations: A&E - Accident and Emergency; ENT - ear/nose/throat; F2F - face-to-face

B.3.5.1.2.3. Medical and technical procedures as part of current BSC

Resource use with regards to medical and technical procedures was also considered as part of the current BSC management of patients with AADC deficiency. Resource use inputs can be found in Section B.3.5.2.2. Table 55 presents costs for medical and technical procedures associated with AADC deficiency, sourced from the National Institute of Reference Costs 2019/2020[114] and the Unit Cost of Health and Social Care 2020 report by the PSSRU[115].

As with BSC treatment and resource use, medical and technical procedures are based on patient motor milestones and are therefore considered for both the BSC arm and the eladocagene exuparvovec arm in the CEA. See Section B.3.5.2.2 for a breakdown of BSC basket composition and resource use inputs per motor milestone health state. These values were based on a survey conducted with European clinical experts (clinical survey, June 2020; see Section B.3.14 for more detail). It is assumed that the BSC treatment, multidisciplinary care and medical and technical procedures continues for the future lifetime of the patients.

Table 55: Unit costs for medical and technical procedures

Resource use	Cost	Source
Barium swallow test	£103.51	National Schedule of Reference Costs 2019/2020: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C)[114]
Blood test	£2.53	National Schedule of Reference Costs 2019/2020 - DAPS05[114]
Coagulation test (PT, INR, PTT)	£2.53	National Schedule of Reference Costs 2019/2020 - DAPS05[114]
Electroencephalography	£371.52	National Schedule of Reference Costs 2019/2020: conventional EEG, EMG or Nerve Conduction Studies, 18 years and under (AA33D)[114]
Folic acid dosage in CSF	£2.53	Assumed equal to blood test

Glycemia NT dosage in CSF	£2.53	Assumed equal to blood test
Iron dosage	£2.53	Assumed equal to blood test
Lumbar puncture	£1,225.78	National Schedule of Reference Costs 2019/2020: weighted average of day case cost for diagnostic spinal puncture (HC72B and HC72C)[114]
MRI (cerebral)	£147.34	National Schedule of Reference Costs 2019/2020: weighted average of MRI scan of one area, without contrast, 18 years and under (RD01B - RD01C)[114]
ECG	£49.00	National Schedule of Reference Costs 2019/2020: Electrocardiogram Monitoring or Stress Testing (EY51Z)[114]
Non-Bruininks-Oseretesky test	£141.00	Assumed equal to occupational therapy appointment
Plasma AADC dosage	£33.80	National Schedule of Reference Costs 2019/2020: special Screening, Examinations or Other Genetic Disorders (WH15Z)[114]
Prolactin dosage	£2.53	Assumed equal to blood test
Urine test	£1.20	Assumed equal to Urine vanillactic test
Urine vanillactic acid level	£1.20	National Schedule of Reference Costs 2019/2020 - DAPS04[114]
X-ray (hip)	£103.51	National Schedule of Reference Costs 2019/2020: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C)[114]
X-ray (pelvis)	£103.51	National Schedule of Reference Costs 2019/2020: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C)[114]
X-ray (spine)	£103.51	National Schedule of Reference Costs 2019/2020: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C)[114]
Upper limb splints	£50.00	Assumption
Lower limb splints	£50.00	Assumption
Manual wheelchair	£103.00	PSSRU 2020: Self or attendant propelled chair (page 88) (Annual cost + maintenance)[115]
Electric wheelchair	£481.00	PSSRU 2020: Powered chair (page 88) (Annual cost + maintenance)[115]
Verticalizers	£50.00	Assumption

Abbreviations: AADC – aromatic L-amino acid decarboxylase; CSF – cerebrospinal fluid; CT - computed tomography; ECG – electrocardiogram; EEG – electroencephalography; INR – international normalized ratio; MRI – magnetic resonance imaging; NT – neurotensin; PT – prothrombin; PTT – partial thromboplastin time

B.3.5.1.3. Summary of annual costs associated with the technology

A summary of the annual cost associated with treatment acquisition, administration, and monitoring in patients in the eladocagene exuparvovec arm is provided in Table 56. The annual cost associated with BSC is considered to be part of the background disease management costs.

Table 56: Costs associated with the technology in the economic model

Items	Eladocagene exuparvovec	BSC
Technology cost	£[redacted]	NA*
Technology administration cost	£2,450.79	£0
Pre- and post-administration cost		
MRI scans	£294.68	-
Paediatric intensive care stay	£3,305.99	-
Paediatric ward stay	£3,064.90	-
Specialist follow-up visits post-surgery	£2,365.12	-
CT scans	£97.23	-
PET scan	£345.88	-
Lumbar puncture	£1,225.78	-
Total annual cost for technology	**£**[redacted]	NA*

**The model conservatively assumes that BSC is associated with no costs as BSC treatments, procedures and resource use are captured in the background disease management costs for each motor milestone health state.*
Please see Table below for the motor milestone health state unit costs. The model also conservatively assumes that BSC is not associated with an administration cost.
Abbreviations: BSC – best supportive care; CEA – cost-effectiveness analysis; CSF – cerebrospinal fluid; CT – computed tomography; PET – positron emission tomography

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1. BSC therapies by motor milestone health state

BSC treatment and resource use is based on motor milestone health state rather than by treatment arm. Table 57 presents the proportion of patients treated with each treatment category in the BSC basket per motor milestone state used in the CEA.

Table 57: BSC treatment use by motor milestone health state

	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Dopamine agonists	89%	89%	75%	86%	86%
MAO inhibitors	67%	67%	50%	86%	86%
Vitamin B6	89%	89%	75%	86%	86%
Anticholinergic agents	11%	11%	0%	0%	0%
Benzodiazepines	33%	33%	0%	0%	0%
Melatonin	44%	44%	0%	30%	30%
Clonidine	0%	0%	0%	0%	0%
L-Dopa	20%	22%	25%	43%	43%
Folic acid (vitamin B9)	67%	67%	25%	14%	14%
Dietary supplement	11%	11%	0%	14%	14%
Vitamin D	0%	0%	0%	0%	0%

Abbreviations: BSC – best supportive care; MAO - monoamine oxidase

B.3.5.2.2. Resource use by motor milestone health state

Resource use inputs are derived from a burden of disease study for AADC deficiency presented in Saberian *et al.* (2021)[112]. The data from the study were adjusted to give the number of visits across all patients in that health state. This was done to ensure that resource use was consistent across the population in the health state as a whole.

The annual number of follow-up visits, hospitalisation, and A&E attendance inputs for each health state are presented in Table 58. It is assumed that these resource use inputs are equal for eladocagene exuparvovec and BSC patients. The resource use inputs by motor milestone health state were validated with clinicians in a clinicians advisory board (Clinical Advisory Board, July 2021).[24]

Table 58: Follow-up visits, hospitalisation, and A&E visits resource use by motor milestone health state

Resource use	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Dietician	1.00	1.00	0.73	0.45	0.45
Endocrinologist	0.00	0.00	0.00	0.00	0.00
Gastroenterologist	1.88	1.88	1.09	0.30	0.30
General practitioner	2.13	2.13	1.79	1.45	1.45

Geneticist	0.00	0.00	0.00	0.00	0.00
Neurologist	2.50	2.50	2.08	1.65	1.65
Nurse	0.00	0.00	0.15	0.30	0.30
Occupational therapy	39.25	39.25	22.23	5.20	5.20
Ophthalmologist	0.75	0.75	0.43	0.10	0.10
Orthopaedic surgeon	0.13	0.13	0.16	0.20	0.20
Otolaryngologist	0.00	0.00	0.05	0.10	0.10
Paediatrician	1.50	1.50	1.55	1.60	1.60
Physiotherapist	84.80	84.80	55.72	26.65	26.65
Pulmonologists	0.00	0.00	0.00	0.00	0.00
Psychiatrist	0.50	0.50	3.33	6.15	6.15
Psychologist	0.00	0.00	0.00	0.00	0.00
Speech therapist	16.31	16.31	26.35	36.40	36.40
Hospitalisation	1.88	1.88	1.39	0.90	0.90
A&E attendance	1.25	1.25	0.63	0.00	0.00

Abbreviations: A&E - Accident and Emergency; ENT - ear/nose/throat

Resource use inputs regarding medical and technical procedures are also taken from the BoD study by Saberian *et al.* (2021)[112] conducted with clinicians and are given in Table 23 and Table 24.

Table 59: Medical procedure annual resource use by motor milestone health state

Medical procedure	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Barium swallow test	0.19	0.19	0.09	0.00	0.00
Blood test	0.88	0.88	0.87	1.00	1.00
Coagulation test (PT, INR, PTT)	0.75	0.75	0.73	0.90	0.90
Electroencephalography	0.75	0.75	0.45	0.10	0.10
Folic acid dosage in CSF	0.00	0.00	0.03	0.03	0.03
Glycemia NT dosage in CSF	0.13	0.13	0.06	0.00	0.00
Iron dosage	0.88	0.88	0.87	1.00	1.00
Lumbar puncture	0.03	0.03	0.04	0.03	0.03
MRI (cerebral)	0.35	0.35	0.26	0.15	0.15
ECG	0.75	0.75	0.88	1.30	1.30
Non-Bruininks-Oseretesky test	0.00	0.00	0.00	0.00	0.00
Plasma AADC dosage	0.00	0.00	0.00	0.03	0.03
Prolactin dosage	1.00	1.00	0.97	1.15	1.15
Urine test	0.75	0.75	0.81	1.00	1.00
Urine vanillactic acid level	0.13	0.13	0.06	0.00	0.00
X-ray (hip)	0.25	0.25	0.13	0.00	0.00
X-ray (pelvis)	0.25	0.25	0.13	0.00	0.00
X-ray (spine)	0.25	0.25	0.23	0.15	0.15

Abbreviations: MRI - magnetic resonance imaging

Table 60: Technical procedure annual resource use by motor milestone health state

Technical procedure	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Upper limb splints	0.00	0.00	0.00	0.00	0.00
Lower limb splints	0.00	0.00	0.00	0.00	0.00
Manual wheelchair	0.06	0.06	0.03	0.00	0.00
Electric wheelchair	0.13	0.13	0.06	0.00	0.00
Verticalizers	0.23	0.23	0.11	0.00	0.00

B.3.5.3 Adverse reaction unit costs and resource use

As is standard for NICE appraisals, the model only considers moderate-to-severe TEAEs. The costs associated with TEAEs are presented in Table 61, with a different cost for moderate and severe events. The costs of TEAEs are sourced from the National Schedule of Reference Costs 2019/2020.[114]

Table 61: Moderate-to-severe TEAE costs

Adverse events	Moderate event cost	Severe event cost	Reference
Dyskinesia	£3,492.73	£5,313.86	National Schedule of Reference Costs 2019/2020 cost for Paediatric Nervous System Disorders, weighted by day case / non-elective short stay by the proportion requiring hospitalisation for moderate and severe dyskinesia (PR01A:E) [114] Moderate: 55% of cases require hospitalisation. Severe: 100% of cases require hospitalisation
Pneumonia	£1,414.61	£2,437.31	National Schedule of Reference Costs 2019/2020: cost for pneumonia (DZ11R and DZ11S for severe and DZ11T and DZ11U for moderate) [114] Moderate: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-9 Severe: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10+
Gastrointestinal disorders	£597.67	£614.03	National Schedule of Reference Costs 2019/2020: day case cost for paediatric gastrointestinal (GI) disorders (PF26A and PF26B for severe and PF26C and PF26D for moderate)[114] Moderate: Paediatric Major Gastrointestinal Disorders with CC Score 1-4 Severe: Paediatric Major Gastrointestinal Disorders with CC Score 5+
Gastroenteritis	£489.90	£565.79	National Schedule of Reference Costs 2019/2020: day case cost for paediatric gastroenteritis (PF21A,PF21B).[114] Moderate: Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 0 Severe: Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 1+

Abbreviations: NHS – National Health Service; TEAE – treatment-emergent adverse events

B.3.5.4 Miscellaneous unit costs and resource use

As described in Section B.3.5.1.1, the introduction of eladocagene exuparvovec is expected to result in some minor changes in the way that current services are run for patients with AADC deficiency in the UK. These are largely associated with the one-off administration of the gene-replacement therapy, which is expected to happen in a single centre in England. The additional costs expected with adoption of eladocagene exuparvovec in the NHS are detailed above in Section B.3.5.1.1.2.

B.3.6. Severity

Not applicable. For highly specialised technologies, the severity of the condition is already implicitly captured in the selection of technologies for evaluations. No additional QALY weighting for the severity of disease is applied.[23]

B.3.7. Uncertainty

The CEA used for this appraisal has limitations driven by the ultra-rare nature of AADC deficiency. Based on a comprehensive literature review conducted by PTC to form the NHDB, only 237 unique patients have been described across the world in the literature. Of these, only 49 unique patients have severity data.[8] UK clinical experts estimate that just [redacted] will be eligible for eladocagene exuparvovec each year over the next 5 years.[5] Given the limited data in the literature, developing a robust, evidence-based CEA in AADC deficiency is extremely challenging and there were no published cost-effective models in AADC deficiency at the time of developing the CEA for this appraisal. Likewise, there are limited utility or survival data specific to AADC deficiency in the literature or in clinical studies.

In addition to a lack of published data in AADC deficiency, the sample sizes of the eladocagene exuparvovec clinical studies used to inform the CEM are small. This is typical of trials in populations with ultra-rare paediatric diseases.

To minimise uncertainty and develop a robust and clinically plausible CEA in AADC deficiency, this CEA was conceptualised based on reviews of NICE appraisals for proxy diseases and/or other HSTs. The CEA leverages insights, assumptions, data and sources accepted by NICE during these appraisals to ensure this AADC deficiency model is centred on approaches critiqued and appraised by NICE. Clear justification for the model approach is made in Section B.3.2.2.

To further inform the model design and minimise uncertainty associated with the limited or lack of data available due to the ultra-rare nature of AADC deficiency, the model structure, approach, inputs and assumptions have been extensively validated and verified with clinical and HEOR experts through numerous advisory boards and clinical validations over the past three years, including a recent validation of the NICE submission with the leading UK clinical experts in AADC deficiency. See Section B.3.14 for more details on the clinical validations.

The following sensitivity analyses were conducted to explore the uncertainty in the model:

- Scenario analyses were conducted to assess the impact of varying inputs in a number of plausible scenarios outlined in Section B.3.11.3 below.
- Deterministic one-way sensitivity analysis (OWSA) on all applicable parameters, using either the upper and lower bounds of 95% confidence intervals, or 20% variation if confidence intervals are unavailable.
- Probabilistic sensitivity analysis (PSA).

The below subsections describe the approaches taken to explore the uncertainty in the CEA.

B.3.7.1 Scenario analyses

Scenario analyses have been explored as part of the CEA. Table 64 summarises the scenario analyses explored, and Table 76 and Table 77 presents the ICER results at list and PAS price, respectively. More detail on select scenarios can be found in the subsections below.

B.3.7.1.1. Length of developmental phase

To take into account initial data analyses indicating that patients are expected to experience a plateau in the development of their motor milestones following treatment with eladocagene exuparvovec, a two-phase model approach was taken: a developmental phase and a long-term phase (see Section B.3.2.2). The length of the developmental phase in the CEA base-case is 12 years following gene-replacement therapy, which aligns with the length of available clinical trial data (9 years in some patients) and considers the possibility that patients can continue to achieve motor milestones up to 16 years of age. A shorter developmental phase duration was explored in sensitivity analysis (Scenario analysis 7 in Table 64).

B.3.7.1.2. Motor milestone achievement in the development phase for eladocagene exuparvovec

AADC deficiency is an ultra-rare disease with wide-ranging symptoms that present heterogeneously across patients. This makes is extremely challenging to robustly model outcomes in AADC deficiency. To overcome data challenges and uncertainty, the CEA assumes that motor milestone achievement is the most important outcome for patients with AADC deficiency and that other outcomes improve as motor function improves (i.e., global symptom improvement). UK clinical experts confirmed that this approach was reasonable.[5,53]

To overcome challenges with the clinical trial data (e.g., varying follow-up duration, small sample size), motor milestones in the eladocagene exuparvovec arm are predicted using PDMS-2 scores, which was the primary outcome in the clinical trials. PDMS-2 is clinically relevant as a measure for motor development in patients with AADC deficiency and is widely used in CP[49,103,120] (the closest disease proxy to AADC deficiency). It is also mentioned in the NICE guidelines for the diagnosis and management of patients with CP[102].

To explore uncertainty associated with the development phase of the model for eladocagene exuparvovec, the following scenario analyses were conducted: using a different Bayesian

model specification (Scenario analysis 6 in Table 64 [Asymptotic distribution]), shortening the length of the developmental phase (Scenario analysis 7 in Table 64 [9 years]) and modelling eladocagene exuparvovec using the motor milestones distribution observed in the AADC deficiency clinical trials (Scenario analysis 8 in Table 64)

B.3.7.1.3. Motor milestone health state curves

Data on mortality for patients with AADC deficiency by motor milestone health state are not available in the literature or in clinical studies. Only [redacted] were reported in clinical studies at the pooled safety data cut (Section B.2.10.7) for eladocagene exuparvovec and the follow-up in some patients is not yet long enough to provide robust survival estimates. Similarly, only 16 deaths were identified in patients with severe AADC deficiency in the NHDB.

To overcome the lack of data and literature on survival of patients with AADC deficiency, CP was used as a proxy disease for survival estimates (based on motor milestones in Brooks *et al.* [2014][92]). There is uncertainty in using Brooks *et al.* (2014)[92] to estimate survival in AADC deficiency patients. Firstly, the motor function health states for CP did not match up exactly with AADC deficiency motor milestone health states in this CEA. Secondly, the average age of death for a patient with CP with no-motor function in the Brooks *et al.* (2014)[92] study appears to be higher than available corresponding data for AADC deficiency. Thirdly, Brooks et al. (2014)[92] report data from a US CP population, which may not be generalisable to the UK. Despite this, Brooks *et al*. (2014)[92] is the most appropriate data source to estimate survival for the following reasons:

1. CP is the closest disease proxy to AADC deficiency, as confirmed in a number of validations with global, European, and UK clinical experts (see Section B.3.14).
2. NICE guidelines for the diagnosis and management of patients with CP[102] consider the patient population in Brooks *et al.* (2014)[92] to be generalisable to the UK.
3. Brooks *et al.* (2014)[92] contains data from 16,440 patients, allowing for parametric survival curves to be fitted to Kaplan Meier data. This method of survival estimation is preferred under NICE methods guidance (NICE DSU 14[123(p14)]).

To explore the uncertainty in survival, the following scenario analysis were conducted: estimating survival using the 2nd best fitting curve overall (Scenario analysis 11 in Table 64 Weibull for all health states except walking with assistance [exponential]), estimating survival using the best fitting curves which do not cross (Scenario analysis 12 in Table 64 [in increasing motor milestones: Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential]) and modelling survival using SMA as a disease proxy through expected survival reported in Oskoui (2007) and Zerres (1997) (Scenario analysis 13 in Table 64).

B.3.7.1.4. Motor milestone health state utility values

HRQoL data were not collected from clinical trials for eladocagene exuparvovec. Therefore, HRQoL data were elicited from a UK TTO study (Smith *et al.* [2021][27]) using five AADC

deficiency motor milestone health state vignettes. The TTO method is aligned with the NICE manual 2022[23] and NICE DSU TSD 11[111].To explore the impact of the HRQoL data on the CEA, scenario analyses explored the use of alternative HRQoL sources derived using SG and DCE methodologies (Section B.3.10.3).

Both the SG and DCE approaches were used with the vignettes developed by Hanbury *et al*. (2021).[56] The SG values[27] were elicited from the same 1,598 UK participants (1,039 congruent responders) who completed the online survey for the TTO. For the SG elicitation, participants were told that there was a cure available to treat the child and return them to "perfect" health, but that there was also a risk that the treatment could fail and lead to "immediate death" of the child. Participants were asked to indicate the level of risk of immediate death they were willing to accept, on a scale of 0 to 100. Health state utilities were then derived by subtracting the participants' response from 100 and dividing the result by 100.

A DCE study by Smith *et al.* (2020)[131] was also conducted to derive utility estimates for specific attributes/characteristics of AADC deficiency. The attributes for the DCE study were identified from the same motor milestone health state vignettes from Hanbury et al (2021)[56]. Six attributes related to AADC deficiency were identified: mobility, muscle weakness, OGC, feeding support, cognitive impairment, screaming. Participants were asked to choose between two alternative health states, which were defined according to a combination of the six attributes. Two scenarios for deriving utility values using DCE were explored. Scenario one involved anchoring the DCE utility values based on the "worst" TTO utility value derived from the TTO study (0.494) and the "best" TTO utility value derived from the TTO study (0.728). Scenario two involved anchoring the DCE utility values based on the "worst" TTO utility value derived from the TTO study (0.494) and perfect health (1). The health state utility values derived from the SG and DCE studies are presented in Table 62. To explore the uncertainty regarding utility values, the following scenario analysis were conducted: SG utility values (Scenario analysis 17 in Table 64), DCE scenario 1 (Scenario analysis 18 in Table 64) and 2 (Scenario analysis 19 in Table 64).

Table 62: Motor milestone state utility values for UK SG and DCE studies

Motor milestone state	SG utility values	DCE utility values scenario 1	DCE utility values scenario 2
No motor function	0.563	0.494	0.494
Full-head control	0.573	0.537	0.586
Sitting unassisted	0.671	0.629	0.785
Standing with support	0.710	0.700	0.940
Walking with assistance	0.749	0.728	1.000

Abbreviations: DCE – discrete choice experiment; SG – standard gamble

B.3.7.1.5. Caregiver disutility

Quantitative caregiver disutilities were not collected from clinical trials. Instead, a review of HSTs identified caregiver disutilities from caregivers of patients with MS, as used in HST 2[95] (MS caregiver EQ-5D disutility values from Acaster *et al.* [2013][28]). To explore the impact of

caregiver disutility on the CEA, a scenario analysis is performed using an alternative source for disutility values (Gani *et al.* [2008][128], which also used MS caregiver EQ-5D disutility values). Values from the study used in the scenario analysis can be found in Table 48. To explore the uncertainty associated regarding caregiver disutility values, the following scenario analysis were conducted: no caregiver disutility (Scenario analysis 20 in Table 64) and using caregiver disutility values from MS from the study by Gani *et al.* (2008)[128] (Scenario analysis 21 in Table 64).

Table 63: Caregiver disutility values

AADC deficiency motor milestone state	Scenario: Gani (2008)
No-motor function	0.11
Full-head control	0.11
Sitting unassisted	0.05
Standing with support	0.05
Walking with assistance	0.00

B.3.7.1.6. Societal perspective

Due to insufficient data available, a societal perspective was not explored as part of the scenario analysis in the CEA. The huge potential societal benefits of eladocagene exuparvovec are summarised in Section B.3.13.

B.3.7.1.7. Summary of scenario analyses

Table 64 presents the scenario analyses explored in the CEA.

Table 64: Summary of scenario analyses in the CEA

Parameter	Base case	Scenario analysis
QALY modifier	Applied	1. Not applied
Discount rate on costs and QALYs	QALYs 1.5%, costs 1.5%	2. QALYs 0%, Costs 0%
		3. QALYs 1.5%, Costs 3.5%
		4. QALYs 3.5%, Costs 1.5%
		5. QALYs 3.5%, Costs 3.5%
Bayesian growth model specification	Gompertz	6. Asymptotic
Length of developmental phase	12 years	7. 9 years
Modelling motor milestones	Bayesian growth modelling of PDMS-2 scores	8. Modelling through observed trial distribution
BSC patient motor milestone achievement	Based on NHDB	9. Assume no improvement for patients on BSC
		10. Assume a 2% probability of improvement in motor milestone state per year in the development phase in the BSC arm
Motor milestone health state survival curves (based on CP data from Brooks 2014)	Best fitting curve: Log-logistic for all health states except walking with assistance [exponential]	11. 2nd best fitting curve overall: Weibull for all health states except walking with assistance (exponential)
		12. Best fitting curves that do not cross (in order by health state: log-logistic, log-logistic, Weibull, log-logistic, exponential)
		13. Using expected survival from SMA instead of CP (Oskoui 2007, Zerres 1997)
Adverse event disutilities and costs	Include both disutilities and costs	14. Exclude adverse events disutilities
		15. Exclude adverse events costs
		16. Exclude adverse events disutilities and costs
Source of motor milestone health state utility values	UK TTO study	17. UK SG study
		18. UK DCE study, scenario 1
		19. UK DCE study, scenario 2
Caregiver disutility	Included	20. Not applied

Source of caregiver disutility values	MS caregivers (Acaster *et al.* (2013))	21. MS caregivers (Gani *et al.* (2008))
Number of caregivers per motor milestone health state	No-motor function 2.20, Full-head control 1.95, Sitting unassisted 1.70, Standing with support 1.45, Walking with assistance 1.20	22. 2.2 caregivers per health state (NICE TA 755 for risdiplam in SMA)

Abbreviations: AADC – aromatic L-amino acid decarboxylase; BSC – best supportive care; CEA – cost effectiveness analysis; CP – cerebral palsy; DCE – discrete choice experiment; MS – multiple sclerosis; NHDB – natural history database; NICE – National Institute for Health and Care Excellence; PDMS-2 – Peabody Developmental Motor Scale Second Edition; QALY – quality adjusted life year; SG – standard gamble; SMA – spinal muscular atrophy; TA – technology appraisal; TTO time-trade off

B.3.7.2 Sensitivity analyses

In addition to scenario analyses, probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) have been carried out in order to explore the uncertainty associated with clinical inputs and variables in the CEA.

B.3.8. Managed access proposal

Not applicable.

B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Table 65: Summary of variables applied in the CEA

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model specification			
Time horizon (years)	Life-time - 100	N/A (fixed values)	B.3.2.2.12, Page 138
Cycle length - long-term phase (months)	3	N/A (fixed values)	
Cost discount rate (%)	1.5	N/A (fixed values)	
Health discount rate (%)	1.5	N/A (fixed values)	
Demographic settings			
Female (%)	50	BETA	B.3.2.1, Page 127
Age (years)	4	NORMAL	
Average patient weight (kg)	11.1	NORMAL	
Clinical inputs			
Developmental phase motor milestone achievement: Eladocagene exuparvovec	See Table 41	N/A (fixed values)	B.3.3.1.1, Page 145
Developmental phase motor milestone achievement: BSC	See Table 42	N/A (fixed values)	B.3.3.1.2, Page 150
Long-term phase: eladocagene exuparvovec and BSC survival	See Table 44	N/A (fixed values)	B.3.3.2, Page 151
Safety			
Dyskinesia incidence, moderate (%)	[redacted]	BETA	B.3.4.4, Page 157
Pneumonia incidence, moderate (%)	[redacted]	BETA	
Gastrointestinal disorders, moderate (%)	[redacted]	BETA	
Gastroenteritis incidence, moderate (%)	[redacted]	BETA	
Dyskinesia incidence, severe (%)	[redacted]	BETA	
Pneumonia incidence, severe (%)	[redacted]	BETA	
Gastrointestinal disorders, severe (%)	[redacted]	BETA	
Gastroenteritis incidence, severe (%)	[redacted]	BETA	
HRQoL (see Table 50)			
No-motor function HSUV	0.494	BETA	B.3.4.5, Page 158

Full-head control HSUV	0.537	BETA	
Sitting unassisted HSUV	0.631	BETA	
Standing with support HSUV	0.676	BETA	
Walking with assistance HSUV	0.728	BETA	
Dyskinesia AE disutility	0.067	BETA	
Pneumonia AE disutility	0.034	BETA	
Gastrointestinal disorders AE disutility	0.051	BETA	B.3.4.4.1, Page 158
Gastroenteritis AE disutility	0.075	BETA	
AE duration (days)	60	GAMMA	
Number of primary caregivers: No motor function	2.200	BETA	
Number of primary caregivers: Full-head control	1.950	BETA	
Number of primary caregivers: Sitting unassisted	1.700	BETA	
Number of primary caregivers: Standing with support	1.450	BETA	
Number of primary caregivers: Walking with assistance	1.200	BETA	
Caregiver disutility: No motor function	0.090	BETA	B.3.4.5.3, Page 160
Caregiver disutility: Full-head control	0.090	BETA	
Caregiver disutility: Sitting unassisted	0.030	BETA	
Caregiver disutility: Standing with support	0.030	BETA	
Caregiver disutility: Walking with assistance	0.000	BETA	
Bereavement disutility	0.037	BETA	
Cost inputs			
Acquisition cost: Eladocagene exuparvovec	£[redacted]	GAMMA	B.3.5.1.1.1, Page 165
Eladocagene exuparvovec admin cost: Intraputaminal administration	£2,450.79	GAMMA	B.3.5.1.1.2, Page 165
Eladocagene exuparvovec admin cost: Pre-operative care	£294.68	GAMMA	
Eladocagene exuparvovec admin cost: Post-operative care	£10,404.90	GAMMA	
Acquisition cost per year: BSC, No motor function	£3,187.37	GAMMA	
Acquisition cost per year: BSC, Full-head control	£3,188.78	GAMMA	B.3.5.1.2, Page 168 B.3.5.2, Page 174
Acquisition cost per year: BSC, Sitting unassisted	£2,200.86	GAMMA	
Acquisition cost per year: BSC, Standing with support	£3,184.30	GAMMA	
Acquisition cost per year: BSC, Walking with assistance	£3,184.30	GAMMA	
Resource and procedures costs per year: BSC, No motor function	£15,633.79	GAMMA	B.3.5.1.2.2, Page 170
Resource and procedures costs per year: BSC, Full-head control	£15,633.79	GAMMA	B.3.5.2, Page 174

Resource and procedures costs per year: BSC, Sitting unassisted	£12,177.09	GAMMA	
Resource and procedures costs per year: BSC, Standing with support	£8,692.90	GAMMA	
Resource and procedures costs per year: BSC, Walking with assistance	£8,692.90	GAMMA	
Dyskinesia AE cost per event, moderate	£3,492.73	GAMMA	B.3.5.3, Page 177
Pneumonia AE cost per event, moderate	£1,414.61	GAMMA	
Gastrointestinal disorders AE cost per event, moderate	£597.67	GAMMA	
Gastroenteritis AE cost per event, moderate	£489.90	GAMMA	
Dyskinesia AE cost per event, severe	£5,313.86	GAMMA	
Pneumonia AE cost per event, severe	£2,437.31	GAMMA	
Gastrointestinal disorders AE cost per event, severe	£614.03	GAMMA	
Gastroenteritis AE cost per event, severe	£565.79	GAMMA	

Abbreviations: AADC – Aromatic L-amino Acid Decarboxylase; AE – adverse event; BSC – Best-supportive care; HRQoL – Health-related quality-of-life; HSUV – health state utility value; NHDB – Natural History Database; PDMS-2 – Peabody Developmental Motor Scales-2.

B.3.9.2 Assumptions

This section provides a summary of the assumptions used in the model.

Table 66: Summary of overall model assumptions

Parameter	Assumption
Efficacy parameters	
Natural history of disease	A small proportion of patients (<5%) who do not receive gene-replacement therapy experience some improvement in motor functioning over their lifetime. Source: Hwu *et al.* (2017)[6] and analysis on the NHDB (data on file). Validated at: HEOR expert advisory board and UK clinical expert validation.[5,53,101]
Treatment efficacy of eladocagene exuparvovec	Eladocagene exuparvovec is expected to improve motor milestone achievement up to a certain timepoint following treatment, after which patients are expected to remain in the same health state in the long-term. Evidence from the currently available individual patient data analyses supports that this is the case. This period in which patients can improve motor milestones is considered as the developmental phase and the duration of this phase is primarily determined through individual patient data analyses. After the developmental phase, patients are not expected to further progress in terms of motor milestone achievement, as suggested by a plateauing in motor milestone achievement from the individual patient data analyses. Patients remain in the same health state for their lifetime. Source: CSRs for AADC-010; AADC-011 and AADC-CU/1601 and individual participant data analysis. Validated at: HEOR expert advisory board.[53,101]
Global symptom improvement	In the model, cognitive functioning of patients and other symptoms such as OGC, dystonia, and other behavioural aspects are assumed to improve as motor milestones improve. This is supported by the clinical trial data, which show that patients treated with eladocagene exuparvovec generally improve in all outcomes measured. Source: Targeted literature review (Section B.3.2.2.8) and individual patient data analyses. Validated at: HEOR expert advisory board[53,101] and the June 2020 clinical advisory board.[5,25] Also validated by a UK clinical expert.[5]
Safety	
Eladocagene exuparvovec	AEs associated with eladocagene exuparvovec are sourced from the clinical trials (TEAEs in AADC-010; AADC-011 and AADC-CU/1601). The CEA captures the disutilities and costs in moderate-to-severe TEAEs that occur in at least 20% of patients.
BSC	The model conservatively assumes that AEs associated with BSC are captured in the health state disease management costs.
AE duration	It is assumed that each AE disutility will last 60 days.

AE cost	It is assumed that each AE is treated as a day case or short hospital stay.
Long-term survival	
Long-term survival of patients with AADC deficiency	Mortality estimates based on motor function in CP patients (Brooks *et al.* [2014])[132] are used to estimate survival in patients with AADC deficiency. A log logistic distribution is used for the no-motor function, full-head control, sitting unassisted and standing with support health states. An exponential distribution is used for the walking with assistance health state in the base case. CP estimates are the optimal source as there is insufficient survival data in patients with severe AADC deficiency and UK and global clinical experts were not able to provide an estimate on AADC deficiency patient survival. CP was identified as the most appropriate proxy disease from a targeted literature search and meetings with global and UK clinical experts. The approach was validated by UK clinical experts[26] and HEOR experts [5,53,101]
Treatments included in the model	
Intervention	The intervention group is eladocagene exuparvovec. In the model, BSC treatment and resource use are dependent on motor milestone health state and so patients treated with eladocagene exuparvovec are conservatively assumed to continue BSC post-gene-replacement therapy.
Comparator	The comparator is BSC, defined as established clinical management without eladocagene exuparvovec (see section B.3.2.3.2 for further details). Source: Wassenberg *et al.* (2017).[2]
Quality-of-life inputs	
Utilities	The model therefore assumes that quality-of-life is dependent on motor milestone health state as there are no EQ-5D or alternative utility data in patients with AADC deficiency specifically. Utilities are derived by TTO from motor milestone health state vignettes. The TTO was completed by UK general population participants.
Carer disutilities	A carer disutility is applied, in line with the NICE manual for health technology evaluations (2022)[23] and consistent with HST 2.[95]
Number of caregivers	It is assumed that patients who achieve higher motor milestones will require less support from caregivers, meaning the caregiver number reduces from the no motor function health state to the walking with assistance health state. This has been validated by UK clinical experts[5] and is consistent with previous HST appraisals with conditions where patients have similar motor impairment.[98]
Resource use	
Resource use inputs	It is assumed that resource use values associated with each motor milestone health state differ, based on clinical expert opinion.[26,5]

Key: AADC – aromatic L-amino decarboxylase; AE – adverse event; BSC – best supportive care; CP – cerebral palsy; CSR – clinical study report; EQ-5D – EuroQoL 5-Dimensions; HEOR – health economics and outcomes research; HRQoL – health-related quality-of-life; HST – highly specialized technology; OGC – oculogyric crisis; TEAE – treatment-emergent adverse event; TTO – time-trade off; UK – United Kingdom

B.3.10. Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

In the base-case, the list price ICER for eladocagene exuparvovec versus BSC is £176,343 per QALY gained. For eladocagene exuparvovec, the total per patient costs are £[redacted], the total per patient LYs gained are [redacted] and the total per patient QALYs gained are [redacted]. Compared with BSC, eladocagene exuparvovec is associated with incremental per patient costs of £[redacted], [redacted] additional LYs, and [redacted] additional QALYs. Because eladocagene exuparvovec is associated with over 10 additional QALYs versus BSC, the QALY modifier is applied in the base case.

When the PAS discount is applied, eladocagene exuparvovec is associated with additional costs of £[redacted] versus BSC, resulting in an ICER of £[redacted] per QALY gained.

The discounted base-case results are presented in Table 67 and undiscounted results are presented in Table 68.

Results with disaggregated costs associated with treatment, adverse events and disease management for both eladocagene exuparvovec and BSC are presented in Table 133 and Table 134 in Appendix J.1.2.

Table 67: Base-case results – List price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	£[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eladocagene exuparvovec	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£176,343

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; LYG – life year gain; QALY – quality-adjusted life year

Table 68: Base-case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	£[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eladocagene exuparvovec	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; LYG – life year gain; PAS – patient access scheme; QALY – quality-adjusted life year

Table 69: Disaggregated costs associated with treatment, adverse events and disease management

	List price			PAS price		
	Eladocagene exuparvovec	**BSC**	**Incremental costs**	**Eladocagene exuparvovec**	**BSC**	**Incremental costs**
Drug acquisition costs						
Total drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs						
Follow-up visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Technical procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events costs						
Dyskinesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; PAS – patient access scheme

B.3.10.2 Net health benefit

In the base-case and using the list price, eladocagene exuparvovec results in a net health benefit (NHB) of -£13.71 versus BSC. In the base case using the PAS discount price, eladocagene exuparvovec results in a NHB of -£[redacted] versus BSC. A positive NHB indicates a product is cost-effective at a given willingness-to-pay threshold.

Table 70: Net health benefit (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000
BSC	£[redacted]	[redacted]	£[redacted]	[redacted]	-£13.71
Eladocagene exuparvovec	£[redacted]	[redacted]			

Abbreviations: BSC – best supportive care; NHB – net health benefit; QALY – quality-adjusted life year

Table 71: Net health benefit (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000
BSC	£[redacted]	[redacted]	£[redacted]	[redacted]	-£[redacted]
Eladocagene exuparvovec	£[redacted]	[redacted]			

Abbreviations: BSC – best supportive care; NHB – net health benefit; PAS – patient access scheme; QALY – quality-adjusted life year

B.3.11. Exploring uncertainty

Given the rarity of AADC deficiency and therefore the challenges of developing a robust model, various sensitivity and scenario analyses are presented below to highlight uncertainties.

B.3.11.1 Probabilistic sensitivity analysis

A PSA was explored in the CEA to explore uncertainty in the results. The PSA jointly samples from the assigned distribution of each model parameter included 1,000 times.

Table 72 summarizes the results from the PSA using the list price of eladocagene exuparvovec. In the PSA using the list price, the ICER is £172,203 per QALY gained for eladocagene exuparvovec versus BSC. The incremental per patient costs with eladocagene exuparvovec versus BSC are £[redacted] and the incremental per patient QALYs gained are [redacted]. The results of each probabilistic model run are presented on the cost-effectiveness plane for eladocagene exuparvovec and BSC (Figure 43 and Figure 44). Figure 45 and Figure 46 present the cost-effectiveness acceptability curves (CEAC) and the cost-effectiveness acceptability frontier (CEAF) using the list price.

Table 73 summarizes the results from the PSA using the PAS discount price of eladocagene exuparvovec. In the PSA using the PAS price, the ICER is £[redacted] per QALY gained for eladocagene exuparvovec versus BSC. The incremental per patient costs with eladocagene exuparvovec versus BSC are £[redacted] and the incremental per patient QALYs gained are [redacted]. The results of each probabilistic model run are presented on the cost-effectiveness plane for eladocagene exuparvovec and BSC (Figure 47 and Figure 48). Figure 49 and Figure 50 present the CEAC and the CEAF using the PAS price.

Table 72:Total costs, QALYs and ICER from the PSA (list price)

	Total costs (95% CI)	Total QALYs (95% CI)	ICER (95% CI)
BSC	[redacted]	[redacted]	-
Eladocagene exuparvovec	[redacted]	[redacted]	£172,203 (£131,245; £228,721)

Abbreviations: BSC – best supportive care; CI – confidence interval; ICER – incremental cost effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

Figure 43: PSA: Total discounted costs and QALYs (list price)

Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 44: PSA: PSA: Incremental costs and QALYs of eladocagene exuparvovec vs BSC (list price)

Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 45: PSA: Multi-way cost-effectiveness acceptability curves (list price)

Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 46: PSA: Cost-effectiveness acceptability frontier (list price)

Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Table 73:Total costs, QALYs and ICER from the PSA (PAS price)

	Total costs (95% CI)	Total QALYs (95% CI)	ICER (95% CI)
BSC			
Eladocagene exuparvovec			

Abbreviations: BSC - best supportive care; CI - confidence interval; ICER - incremental cost effectiveness ratio; PAS - patient access scheme; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 47: PSA: Total discounted costs and QALYs (PAS price)

Abbreviations: BSC - best supportive care; CI - confidence interval; ICER - incremental cost effectiveness ratio; PAS - patient access scheme; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 48: PSA: Incremental costs and QALYs of eladocagene exuparvovec vs BSC (PAS price)

Abbreviations: BSC – best supportive care; CI – confidence interval; ICER – incremental cost effectiveness ratio; PAS – patient access scheme; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

Figure 49: PSA: Multi-way cost-effectiveness acceptability curves (PAS price)

Abbreviations: BSC – best supportive care; CI – confidence interval; ICER – incremental cost effectiveness ratio; PAS – patient access scheme; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

Figure 50: PSA: Cost-effectiveness acceptability frontier (PAS price)

Abbreviations: BSC – best supportive care; CI – confidence interval; ICER – incremental cost effectiveness ratio; PAS – patient access scheme; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

B.3.11.2 Deterministic sensitivity analysis

To identify key parameters influencing the model results, a one-way sensitivity analysis (OWSA) was conducted in which applicable parameters were varied by either using the upper and lower bounds of 95% confidence intervals or +/- 20% if confidence intervals are unavailable.

Using the list price Figure 51 and Figure 52 present the impact on incremental QALYs and incremental costs from the OWSA for eladocagene exuparvovec versus BSC. Figure 53 presents the impact on the ICER from the OWSA for eladocagene exuparvovec.

Using the PAS discount price Figure 54 and Figure 55 present the impact on incremental QALYs and incremental costs from the OWSA for eladocagene exuparvovec versus BSC. Figure 56 presents the impact on the ICER from the OWSA for eladocagene exuparvovec.

Table 74 and Table 75 show the results for the top 10 most sensitive parameters from the OWSA. It should be noted that inputs for the Bayesian growth model could not be included in the OWSA due to challenges implementing them in an OWSA. They are still included in the PSA.

The main drivers of the incremental QALYs are the caregiver disutility for patients with no motor function or full-head control, as well as the patient utility for patients in the standing with support, sitting unassisted and no-motor function health states. The main drivers of the incremental costs are BSC resource use for patients with no motor function, including occupational therapy, physiotherapist, and hospitalization. Other key driver includes the eladocagene exuparvovec-related occupational therapy costs for patients in the sitting and no motor function milestone achievement health states.

The main drivers of the ICER are caregiver disutilities for patients in the no-motor function and full-head control categories, as well as utility values for the standing with support, sitting unassisted and no-motor function motor milestone health states.

Figure 51: OWSA: Eladocagene exuparvovec vs. BSC: Incremental QALYs (list price)

Abbreviations: BSC – best supportive care; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; Util - utilities

Figure 52: OWSA: Eladocagene exuparvovec vs. BSC: Incremental costs (list price)

Abbreviations: BSC – best supportive care; FHA – full head control; NMF – no motor function; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use

Figure 53: OWSA: Eladocagene exuparvovec vs. BSC: ICER (list price)

Abbreviations: BSC – best supportive care; FHA – full head control; ICER – incremental cost-effectiveness ratio; NMF – no motor function; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use; Util – utilities

Table 74: OWSA most sensitive parameters for ICER impact (list price)

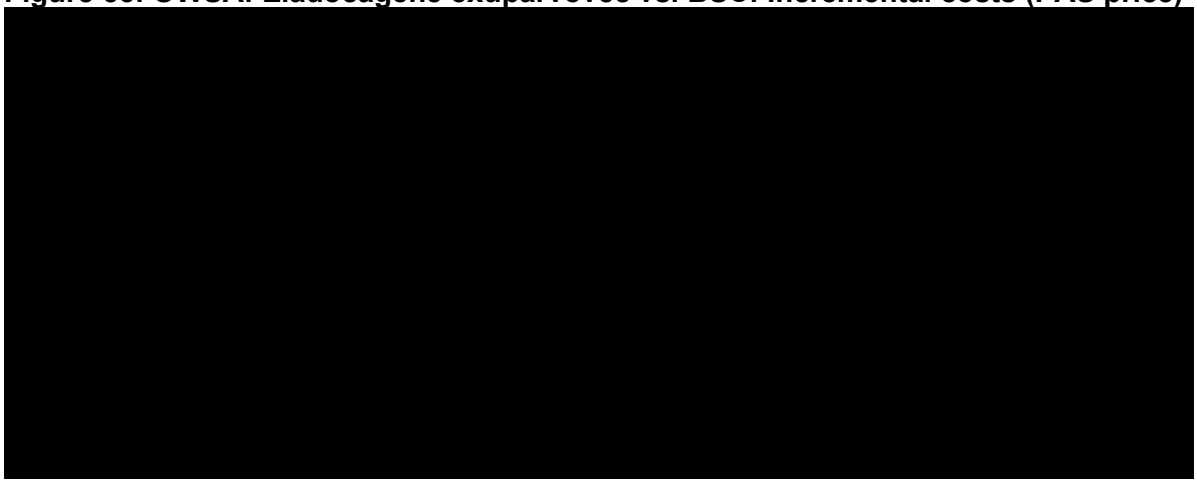
Parameter	Lower	Upper	Difference
Caregiver disutility: No motor function	£	£	£
Util: No-motor function	£	£	£
Util: Standing with support	£	£	£
Util: Sitting unassisted	£	£	£
Util: Walking with assistance	£	£	£
Caregiver disutility: Full-head control	£	£	£
Caregiver disutility: Standing with support	£	£	£
Caregiver disutility: Sitting unassisted	£	£	£
Util: Full-head control	£	£	£
NMF BSC: RU Occupational therapy	£	£	£

Abbreviations: BSC – best supportive care; FHA – full head control; ICER – incremental cost-effectiveness ratio; NMF – no motor function; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use; Util – utilities

Figure 54: OWSA: Eladocagene exuparvovec vs. BSC: Incremental QALYs (PAS price)

Abbreviations: BSC – best supportive care; FHA – full head control; NMF – no motor function; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use

Figure 55: OWSA: Eladocagene exuparvovec vs. BSC: Incremental costs (PAS price)



Abbreviations: BSC – best supportive care; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; Util – utilities

Figure 56: OWSA: Eladocagene exuparvovec vs. BSC: ICER (PAS price)

Abbreviations: BSC – best supportive care; ICER – incremental cost-effectiveness ratio; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use; Util – utilities

Table 75: OWSA most sensitive parameters for ICER impact (PAS price)

Parameter	Lower	Upper	Difference
Caregiver disutility: No-motor function	£	£	£
Util: No-motor function	£	£	£
Util: Standing with support	£	£	£
Util: Sitting unassisted	£	£	£
Util: Walking with assistance	£	£	£
Caregiver disutility: Full-head control	£	£	£
Caregiver disutility: Standing with support	£	£	£
Caregiver disutility: Sitting unassisted	£	£	£
NMF BSC: RU Occupational therapy	£	£	£
NMF BSC: RU Physiotherapist	£	£	£

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; NMF – no motor function; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use; Util – utilities

B.3.11.3 Scenario analysis

As described in Section B.3.7.1, a number of scenarios were explored to investigate the impact of using different assumptions, values, and data sources for model inputs. The results of the scenario analysis are presented in Table 76 and Table 77 using the list and PAS price, respectively. The scenario analysis show that the CEA is most sensitive to the QALY modifier and discount rate on cost and QALYs.

Table 76: Scenario analysis results (list price)

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
Base case	-	£[redacted]	[redacted]	**£176,343**
QALY modifier applied	QALY modifier not applied	£[redacted]	[redacted]	£[redacted]
Discount rate - QALYs: 1.5%, costs: 1.5%	Discount rate - Costs: 0%, QALYs: 0%	£[redacted]	[redacted]	£[redacted]
	Discount rate - Costs: 3.5%, QALYs: 1.5%	£[redacted]	[redacted]	£[redacted]
	Discount rate - Costs: 1.5%, QALYs: 3.5%	£[redacted]	[redacted]	£[redacted]
	Discount rate - Costs: 3.5%, QALYs: 3.5%	£[redacted]	[redacted]	£[redacted]
Model specification: Gompertz (28 patients)	Model specification: Asymptotic (28 patients)	£[redacted]	[redacted]	£[redacted]
Length of developmental phase: 12 years	Length of developmental phase: 9 years	£[redacted]	[redacted]	£[redacted]
Modelling motor milestones through Bayesian growth model	Modelling motor milestones though observed distribution	£[redacted]	[redacted]	£[redacted]
Development based on NHDB	NHDB-based development: No improvement for patients on BSC	£[redacted]	[redacted]	£[redacted]
	NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	£[redacted]	[redacted]	£[redacted]
Expected survival (Brooks 2014): CP. Best fitting curve: Log-logistic for all health states except walking with	2nd best fitting curve overall: Weibull for all health states except walking with assistance (exponential)	£[redacted]	[redacted]	£[redacted]

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
assistance [exponential])	Best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	£[redacted]	[redacted]	£[redacted]
	Expected survival (Oskoui 2007, Zerres 1997): SMA	£[redacted]	[redacted]	£[redacted]
Include adverse event (both disutilities and costs)	Exclude adverse events disutilities	£[redacted]	[redacted]	£[redacted]
	Exclude adverse events costs	£[redacted]	[redacted]	£[redacted]
	Exclude adverse events disutilities and costs	£[redacted]	[redacted]	£[redacted]
Source of utility: TTO study (UK)	Source of utility: SG study (UK)	£[redacted]	[redacted]	£[redacted]
	Source of utility: DCE study (UK), scenario 1	£[redacted]	[redacted]	£[redacted]
	Source of utility: DCE study (UK), scenario 2	£[redacted]	[redacted]	£[redacted]
Caregiver disutility applied	No caregiver disutility	£[redacted]	[redacted]	£[redacted]
Caregiver disutility source: Acaster (2013)	Source: Gani *et al.* (2008)	£[redacted]	[redacted]	£[redacted]
Numbers of caregivers per health state: No-motor function 2.20, Full-head control 1.95, Sitting unassisted 1.70, Standing with support 1.45, Walking with assistance 1.20	2.2 caregivers per health state	£[redacted]	[redacted]	£[redacted]

Abbreviations: AADC – aromatic L-amino acid decarboxylase; BSC – best supportive care; CEA – cost effectiveness analysis; CP – cerebral palsy; DCE – discrete choice experiment; ICER – incremental cost-effectiveness ratio; MS – multiple sclerosis; NHDB – natural history database; NICE – National Institute for Health and Care Excellence; PDMS-2 – Peabody Developmental Motor Scale Second Edition; QALY – quality adjusted life year; SG – standard gamble; SMA – spinal muscular atrophy; TA – technology appraisal; TTO time-trade off

Table 77: Scenario analysis results (PAS price)

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
Base case	-	£[redacted]	[redacted]	£[redacted]
QALY modifier applied	QALY modifier not applied	£[redacted]	[redacted]	£[redacted]
Discount rate - QALYs: 1.5%, costs: 1.5%	Discount rate - Costs: 0%, QALYs: 0%	£[redacted]	[redacted]	£[redacted]
	Discount rate - Costs: 3.5%, QALYs: 1.5%	£[redacted]	[redacted]	£[redacted]

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
	Discount rate - Costs: 1.5%, QALYs: 3.5%	£[redacted]	[redacted]	£[redacted]
	Discount rate - Costs: 3.5%, QALYs: 3.5%	£[redacted]	[redacted]	£[redacted]
Model specification: Gompertz (28 patients)	Model specification: Asymptotic (28 patients)	£[redacted]	[redacted]	£[redacted]
Length of developmental phase: 12 years	Length of developmental phase: 9 years	£[redacted]	[redacted]	£[redacted]
Modelling motor milestones through Bayesian growth model	Modelling motor milestones though observed distribution	£[redacted]	[redacted]	£[redacted]
Development based on NHDB	NHDB-based development: No improvement for patients on BSC	£[redacted]	[redacted]	£[redacted]
	NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	£[redacted]	[redacted]	£[redacted]
Expected survival (Brooks 2014): CP. Best fitting curve: Log-logistic for all health states except walking with assistance [exponential])	2nd best fitting curve overall: Weibull for all health states except walking with assistance (exponential)	£[redacted]	[redacted]	£[redacted]
	Best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	£[redacted]	[redacted]	£[redacted]
	Expected survival (Oskoui 2007, Zerres 1997): SMA	£[redacted]	[redacted]	£[redacted]
Include adverse event (both disutilities and costs)	Exclude adverse events disutilities	£[redacted]	[redacted]	£[redacted]
	Exclude adverse events costs	£[redacted]	[redacted]	£[redacted]
	Exclude adverse events disutilities and costs	£[redacted]	[redacted]	£[redacted]
Source of utility: TTO study (UK)	Source of utility: SG study (UK)	£[redacted]	[redacted]	£[redacted]

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
	Source of utility: DCE study (UK), scenario 1	£[redacted]	[redacted]	£[redacted]
	Source of utility: DCE study (UK), scenario 2	£[redacted]	[redacted]	£[redacted]
Caregiver disutility applied	No caregiver disutility	£[redacted]	[redacted]	£[redacted]
Caregiver disutility source: Acaster (2013)	Source of caregiver disutility: Gani *et al.* (2008)	£[redacted]	[redacted]	£[redacted]
Numbers of caregivers per health state: No-motor function 2.20, Full-head control 1.95, Sitting unassisted 1.70, Standing with support 1.45, Walking with assistance 1.20	2.2 caregivers per health state	£[redacted]	[redacted]	£[redacted]

Abbreviations: AADC – aromatic L-amino acid decarboxylase; BSC – best supportive care; CEA – cost effectiveness analysis; CP – cerebral palsy; DCE – discrete choice experiment; ICER – incremental cost-effectiveness ratio; MS – multiple sclerosis; NHDB – natural history database; NICE – National Institute for Health and Care Excellence; PAS – patient access scheme; PDMS-2 – Peabody Developmental Motor Scale Second Edition; QALY – quality adjusted life year; SG – standard gamble; SMA – spinal muscular atrophy; TA – technology appraisal; TTO time-trade off

B.3.12. Subgroup analysis

Due to the rarity of the AADC deficiency and very limited clinical trial sample size (N=28 patients treated with eladocagene exuparvovec), no subgroup analyses were performed in any of the three individual studies.

B.3.13. Benefits not captured in the QALY calculation

As described in B.1.3, AADC deficiency is a very severe condition involving a wide range of severe and debilitating symptoms that impact patients from birth and throughout their shortened lives. Without gene-replacement therapy, over 95% of patients with severe AADC deficiency (i.e. poor or no head control at 2 years of age) are expected to live their entire life with no motor function and are completely dependent on caregiver support.[8]

Compared with a lifetime of no motor function and severe symptoms, patients treated with eladocagene exuparvovec are able to achieve key motor milestones (e.g. walking with assistance), and experience improvements in all other symptoms including a reduction in OGCs and improvement in cognition and language (see Section B.2). The profound and life-changing benefit of eladocagene exuparvovec can be seen in patient videos in Tai *et al.* (2022)[68] and provided as part of patient and caregiver interviews (please see the EMA Scientific Advisory Group video of patient 311, which shows a video of a patient who is able to walk and talk aged 3 years and 7 months (two years after eladocagene exuparvovec)).

While some of the benefits of eladocagene exuparvovec are captured in the QALY calculations in Section B.3.10, the gene-replacement therapy is likely to also offer benefits not captured in QALY calculations, including:

- Societal benefits from increased caregiver and patient work productivity
- Savings to other government bodies through reduced financial support for affected families.
- A reduction in the need in specialist disability equipment at home and home modifications, for example, improved access in corridors and rooms and installation of ramps, which may be paid for by local social services, supported via government grants, such as the Disabled Facilities Grant or even paid for by families themselves to improve the safety and comfort of the patient with AADC-c.

B.3.13.1 Benefits of the technology outside of the NHS and personal social services

Caring for a patient with AADC deficiency is extremely challenging. As described in Section B.1.3.7, caregivers are reported to spend on average 13 hours per day on practical and emotional care, and 15 hours per week on administrative tasks (e.g. traveling to healthcare appointments),[13] indicating round-the-clock care for their child with AADC deficiency. This impacts caregiver employment, with 75% of caregivers reporting that they have stopped working or reduced their working hours.[13] Caregivers of patients with AADC deficiency report the following:

"It's pretty much nonstop, so I can't have a social life… so no social life… pretty much no leisure activities"[61]

"My life is schedule[d] minute by minute. I have to plan things, I cannot miss one hour, I panic, I get paranoid, because I have to do this and that"[61]

"It's very difficult, emotionally it's very heavy, psychologically heavy, and what else can I say, and then my life as well, I don't want to be misinterpreted, because in a way, my life has changed, my life it's not the life I wanted to have with my son"[11]

By improving patient motor function and AADC deficiency symptoms, eladocagene exuparvovec is likely to reduce the caregiver burden of AADC deficiency and in turn generate societal benefits from allowing caregivers to pursue employment. In a survey of caregivers of patients with AADC deficiency, higher motor milestone achievement in the patient was linked to lower caregiver burden.[11] For example, caregivers of patients who could walk with assistance were better able to participate in social and leisure activities.[11] Eladocagene exuparvovec is also likely to improve caregivers' emotional well-being, social lives, education, and finances by reducing the caregiver burden. Given that each patient requires at least 2

family caregivers, eladocagene exuparvovec is likely to generate life-changing benefits for the families of treated patients.

In addition to caregiver benefits, eladocagene exuparvovec may provide additional benefits to patients. While it is too early to tell if patients treated with eladocagene exuparvovec are able to pursue paid employment, the improvement seen in some patients (as displayed in patient videos in Tai *et al.* (2022)[68] and patient videos [please see the EMA Scientific Advisory Group video of patient 311])[19] suggests that patients can achieve near full-health following gene-replacement therapy. This may mean they are able to pursue employment and therefore generate societal benefits. In addition, patients will experience improvements in their social lives and education following eladocagene exuparvovec.

B.3.13.2 Benefits of the technology to government bodies other than the NHS

As stated in Section B.1.3, AADC deficiency is associated with a profound burden to patients and caregivers. Most patients live their entire shortened life with no motor function and a wide range of severe symptoms and require round-the-clock caregivers support from family caregivers. This means that families with a child affected by AADC deficiency are likely to require financial assistance to cover child tax benefits, disability allowance, carer allowance and income support. This financial assistance is provided by various UK governmental bodies, including the Departments for Work and Pensions, Education, Health and Social Care, and Communities, as well as Local Government and County Councils. By improving patient outcomes and therefore reducing the caregiver need for governmental financial support, eladocagene exuparvovec may generate savings to UK governmental bodies.

B.3.13.3 Out-of-pocket savings to patients and caregivers

Patients with AADC deficiency and their caregivers are expected to face huge financial challenges in terms of out-of-pocket costs:

- Family caregivers give up employment to care for patients with AADC deficiency, with 75% of caregivers reporting that they either stop working or reduce their hours.[13]
- Given that AADC deficiency is an ultra-rare disease, patients and caregivers may be required to travel long distances to see specialists. Caregivers of patients with AADC deficiency report spending 15 hours a week on administration duties (e.g. traveling to appointments).[13] If the specialist centre is particularly far from the family home, families may also need to pay for overnight accommodation in addition to the travel costs.
- Home adaptions and assistive devices are needed to care for patients with AADC deficiency. While some of these costs are borne by the NHS, some may not be. In the NICE appraisal (HST 18) for an analogous disease (metachromatic leukodystrophy (MLD)), it was noted that families self-fund £30,000 for home modifications, £13,200 per year for specialist care, and over £16,000 on other items to support the child.[99] Similar self-funding may be expected for families affected by AADC deficiency.

By providing life-long and meaningful benefits to patients, eladocagene exuparvovec may reduce patient out-of-pocket costs associated with AADC deficiency.

B.3.13.4 Caregiver time savings

As stated in B.1.3.7, caregivers of patients with AADC deficiency report that they provide round-the-clock care. In a survey of 14 caregivers of 13 patients with AADC deficiency, it was reported that caregivers spend on average 13 hours per day supporting their child with practical and emotional care, and 15 hours per week on administrative tasks.[13] Caregivers of patients with AADC deficiency report the following:

"It's pretty much nonstop, so I can't have a social life… so no social life… pretty much no leisure activities"[61]

"My life is schedule[d] minute by minute. I have to plan things, I cannot miss one hour, I panic, I get paranoid, because I have to do this and that"[61]

"It's very difficult, emotionally it's very heavy, psychologically heavy, and what else can I say, and then my life as well, I don't want to be misinterpreted, because in a way, my life has changed, my life it's not the life I wanted to have with my son"[11]

"The negatives, of course, you don't want to see your child have to struggle…there's been times where I have been super depressed"[11]

"I'm anxious always, I think this is something that will die with me because anxiety doesn't make me sleep at night, that doesn't allow me to put my son in the other room, I'm anxious. I'm scared something could happen, I'm not ready to help him if something happens"[11]

"We [my husband and I] were quite distant at a physical level and we weren't talking much, we were not on the same track… my concern was not any more a husband and a marriage, I was concentrating on other things"[61]

This highlights the huge emotional and lifestyle challenges of supporting a child with AADC deficiency. As highlighted in patient videos (see Tai et al 2022[68] and the EMA Scientific Advisory Group video of patient 311, eladocagene exuparvovec provides life-changing benefits to caregivers by improving patient outcomes. This in turn is expected to allow reduce the time needed by caregivers to support their child, allowing the caregivers to pursue social and leisure activities. It will also improve the quality of the time spent caring for patients, as patients will be able to interact with their family caregivers. The happy moments from watching a child improve following gene-replacement therapy may also improve family relationships.

B.3.13.5 Benefit of the technology to the AADC deficiency evidence base

As stated throughout this submission, AADC deficiency is an ultra-rare, severe, and highly heterogeneous disease with very limited published data on patient natural history and no currently approved disease-modifying therapies.

By introducing eladocagene exuparvovec in UK practice, clinical experts in the UK will gain first-hand, real-world experience delivering gene-replacement therapy to patients with AADC deficiency. The insights collected from patients following treatment will help to inform the optimal management of patients with AADC deficiency. As the UK includes some of the world-leading experts in AADC deficiency, real-world UK experience will further help position the UK as a leading country in managing patients with AADC deficiency. Notably, it is expected that patients from other countries (e.g. Ireland and Scandinavia) may be sent to the UK to receive eladocagene exuparvovec, further strengthening the UK's position as world leaders in rare paediatric neurometabolic disorders. The insights and experience from delivering eladocagene exuparvovec treatment can also pave the way for similar innovations in future, while the availability of eladocagene exuparvovec could also lead to improvements in the diagnosis of patients with AADC deficiency in the UK, further improving patient outcomes.

To support with disease understanding and understanding of the technology's effectiveness, PTC Therapeutics is in the process of establishing a patient registry to collect data on patients with AADC deficiency treated with eladocagene exuparvovec in the real-world (PTC-AADC-MA-406).[30] Patients treated in the UK are expected to be enrolled into the registry and the objectives are to understand the natural history of disease (i.e. before eladocagene exuparvovec), and to monitor outcomes following real-world use of eladocagene exuparvovec. Please see Section B.3.13.7 for more information.

B.3.13.6 Benefit of the technology to UK innovation

As the first gene replacement therapy for patients with AADC deficiency and the first disease-modifying option, eladocagene exuparvovec is a significant innovation and step-change in the optimal management of patients with AADC deficiency. It will be the first and only licensed treatment that addresses the underlying biological cause of this severe and life-limiting disease. Through a one-time administration, eladocagene exuparvovec is expected to provide transformative, life-changing benefits to patients and their families.

As stated in Section B.3.13.5 above, the availability of eladocagene exuparvovec in the UK will help to optimize the provision of care to patients with AADC deficiency in the UK. It will allow the UK's specialist centres (including GOSH) to improve their first-hand experience of specialized delivering gene-replacement therapy using stereotactic neurosurgery in patients. Furthermore, it will help to solidify knowledge among the UK's clinical expert community, who are among the world leaders in AADC deficiency. Patients from other countries (e.g. Ireland and Scandinavia) are expected to be sent to the UK to receive gene-replacement therapy, further enhancing UK knowledge and the reputation of the UK specialist centers. The clinical

experience gained from delivering eladocagene exuparvovec should pave the way for future similar innovations.

By recommending eladocagene exuparvovec in the England and Wales, the NHS and NICE can also demonstrate their capabilities in making the most innovative therapies available and can highlight their commitment to supporting innovation in ultra-rare conditions. In turn, the UK can demonstrate its commitment to offering much-needed hope and benefits to children and families affected by this severe and devastating condition.

B.3.13.7 AADCAware patient registry

PTC Therapeutics is committed to delivering life-changing innovations to patients with ultra-rare diseases, such as AADC deficiency. To support the continued understanding of the benefits of eladocagene exuparvovec in real-world practice, PTC is in the process of establishing a patient registry (AADCAware; PTC-AADC-MA-406).[30] The registry is expected to include patients treated with eladocagene exuparvovec in the UK, as well as patients from the US, Italy, Germany, France, Spain, Brazil, Israel, Turkey, and Saudi Arabia.[30]

AADCAware is a two-part, international, multicenter, longitudinal, real-world, observational registry consisting of participants diagnosed with AADC deficiency (Part A) and participants treated with eladocagene exuparvovec (Part B).[30] In Part A, patients with a diagnosis of AADC deficiency will be enrolled and followed up to the point of receiving gene-replacement therapy, to describe the natural history of AADC deficiency in patients treated with BSC (i.e. before gene-replacement therapy).[30] In Part B, patients will be followed-up for a minimum of 10 years to assess the long-term safety and effectiveness of eladocagene exuparvovec.[30] Outcomes collected include motor milestones and motor function, quality-of-life, and symptoms of AADC deficiency (e.g. infections, feeding, body weight, OGC).[30] Endpoints of interest include PDMS-2 score, Gross Motor Function Measure-88 (GMFM-88), Bayley-III, OGC, EQ-5D, and AEs.[30] Interim analyses are planned at least every year, meaning regular updates on the natural history of AADC deficiency and on real-world outcomes following treatment with eladocagene exuparvovec.

B.3.13.8 Expertise and infrastructure required to deliver the technology

Eladocagene exuparvovec is administered via stereotactic neurosurgery involving bilateral infusion to the putamen region of the brain. While it is an innovative and highly specialised technology, the specialist centres expected to deliver eladocagene exuparvovec are understood to already have the infrastructure and expertise to deliver the technology. To ensure optimal implementation of the technology, PTC Therapeutics is delivering comprehensive training to the specialist centres, including mock surgeries and educating key stakeholders on the optimal pre-, peri-, and post-surgical care of patients treated with eladocagene exuparvovec.

B.3.14. Validation

Given the challenges of modelling AADC deficiency, the CEA has been validated multiple times at different stages in its development, from conceptualisation through to the final UK base case.

B.3.14.1 Clinical expert advisory board 1: February 2020

An advisory board was held on 20 February 2020 to obtain input on the HRQoL and utility of AADC deficiency patients and obtain advice on the CEM from clinical experts.[26] As no previous CEAs had been published for AADC deficiency or eladocagene exuparvovec at the time the advisory board was conducted, the advisory board was the first step in allowing clinical experts to inform the structure of the CEA and describe the health state vignettes for utility elicitation. The advisory board objectives included:

- To obtain feedback on the proposed methods to capture HRQoL and utility elicitation
- To obtain input on the vignette attributes and their impact on patients and caregivers
- To validate if the proposed draft CEA accurately represents the patient journey
- To understand how to capture disease severity in the model
- To gain clarity on which disease states should be included in the model in the context of potential efficacy outcomes of a gene-replacement therapy treatment
- To get input on addressing potential data gaps in the CEA

The advisory board included five clinical experts with experience managing patients with AADC deficiency. Three were from France, one was from Portugal, and one was from Spain:

[redacted]

The advisory board validated the approach to focus the model on motor milestone health states and confirmed that global symptom improvement would be expected (see Section B.3.2.2.8). It also confirmed that there are limited robust survival estimates in AADC deficiency and identified SMA and CP as appropriate proxy diseases for survival estimates (see Section B.3.3.2). The advisory board also validated and informed motor milestone health state vignettes for the derivation of utility values (see Section B.3.4.5).

B.3.14.2 Clinical survey: June 2020

A clinician survey was conducted on 5 June 2020 to validate CEA assumptions and test value messages.[25] The clinician survey was the second session after the clinician advisory board held in February 2020. The survey was conducted with 25 clinical experts with experience managing paediatric neurometabolic disorders, with most respondents having AADC deficiency experience.

CEM assumptions were validated in a 2-step process: (1) a pre-advisory board survey available to 25 clinicians and answered by 21 clinicians, and (2) a post- advisory board survey available to 24 clinicians and answered by 21 clinicians. Of the 21 clinicians who participated in the pre-advisory board survey, eight were based in Europe, seven in South America, three in the Middle East, two in the United States, and one in Asia. Of the 21 clinicians who participated in the post-advisory board survey, eight were based in Europe, nine in South America, one in the Middle East, two in the United States, and one in Asia.

The clinical survey contributed to the validation of using CP as a disease proxy for AADC deficiency for survival estimates (see Section B.3.3.2) and the assumption that BSC and resource use is expected to vary by motor milestones (see Section B.3.5.2.2).

B.3.14.3 Economic advisory board 1: March 2021

An economic model validation meeting was held with HEOR experts on March 2021.[53] The objectives of the March 2021 economic model validation panel were to validate the assumptions used for the CEA and to discuss solutions to minimise the uncertainty caused by lack of data. The economic advisory board was the third consultation used to validate the CEM (after the clinician advisory board held in February 2020 and the clinician survey held in June 2020) and the validation focused primarily on the economic aspects of the model.

The following model characteristics were interrogated:

- Model structure
- Developmental phase of the model
- Long term phase of the model
- Natural history data

The panel discussion was conducted as an online workshop divided into 2 sessions of 2 hours in length, taking place on successive weeks. The validation panel included eight experts in health economics; two from France, two from the UK, one from Italy, one from Norway, one from Sweden, and one from Brazil.

All participants reported previous experience working with economics models for rare diseases (including SMA, haemophilia, severe combined immunodeficiency, CP, DMD, Fabry, Pompe, Gaucher, familial amyloid polyneuropathy. Three of the participants reported previous experience with advanced therapy medicinal products.

Prior to the first session, the panel were provided a 20-page pre-read dossier that described the disease area and gave an overview of the model structure and key assumptions.

The economic advisory board contributed to the validation of the model structure (see Section B.3.2.2), including the developmental and long-term phase of the model, survival estimates used in the model (see Section B.3.3.2), and the NHDB used for the cohort of patients receiving BSC in the comparator arm of the model (see Section B.2.9).

B.3.14.4 Clinical expert advisory board 2: July 2021

A scientific committee meeting was held with three clinical experts with experience managing AADC deficiency in France on July 2021.[24] The objective of the July 2021 scientific committee meeting was to discuss the methodological choices for the CEM, including:

- Efficacy estimation
- Survival estimation
- Healthcare resource use
- Utility estimation

The scientific committee meeting included three clinical experts from France;

[redacted]

The clinician advisory board contributed to the validation of the comparator data source, structural choices in the model (see Section B.3.2.2), and resource use of patients with AADC deficiency (see Section B.3.5.2).

B.3.14.5 UK clinical expert consultation: March-April

The UK clinical validation consultation was held through March and April 2022.[5] The objectives of the March-May 2022 consultation were to:

- Understand the clinical management of patients with AADC deficiency in the UK
- Validate clinical effectiveness evidence in the NICE submission
- Validate cost-effectiveness evidence in the NICE submission
- Ensure the NICE submission accurately reflects the UK management of AADC deficiency

There are very few clinical experts in the UK with experience managing patients with AADC deficiency. Despite this, individual consultations were held with two of the UK's leading clinical experts in AADC deficiency:

[redacted]

[redacted]

The validations were conducted over two separate virtual interviews with each clinician. Prior to the first session, each clinician was provided with pre-read materials that described the epidemiology of AADC deficiency, the clinical trials for eladocagene exuparvovec, the CEA structure, mortality of patients with AADC deficiency, resource use of patients with AADC deficiency, and the caregiver burden of AADC deficiency.

The UK clinical validation consultation contributed to the validation and inputs for:

- Efficacy estimation
- Disease proxies
- Survival estimation
- Healthcare resource use
- Caregiver burden

Notably, UK clinical experts confirmed that severe AADC deficiency is ultra-rare (maximum [redacted] per year expected in England and [redacted] every [redacted] expected in Scotland). Of [redacted] patients with AADC deficiency managed by the clinical experts in the UK, [redacted] had poor or no head control. UK clinical experts confirmed that patients with severe AADC deficiency have a very poor prognosis with no or very limited improvements in motor function over their lifetime when treated with current BSC.

UK experts were unable to provide an accurate estimate of patient survival but confirmed that survival estimates in AADC deficiency are limited in the literature and that patients are expected to die before they reach their teenage years. Of the [redacted] patients with severe AADC deficiency in the UK seen by the UK experts, the age at death was stated to be [redacted] years in those who have died. One clinician stated that there is a higher risk of mortality in the first 0-20 years in life with an even higher risk in childhood. In the absence of suitable literature on AADC deficiency survival, UK clinical experts agreed that, while not perfect, CP was the best proxy for AADC deficiency and a better proxy than SMA.

UK experts confirmed that motor function is the key outcome in patients with AADC deficiency and accepted that other symptoms of AADC deficiency may be expected to improve as motor function improves (i.e. global symptom improvement).

In terms of clinical management of AADC deficiency, UK experts broadly agreed with the treatment types stated in Wassenberg et al (2017) and the proportion treated with each therapy according to the AADC deficiency clinician survey. Likewise, UK experts broadly agreed that the multidisciplinary team of specialist visits used in the CEA were in line with those in UK practice. UK experts agreed that BSC treatment and specialist use would reduce as patient motor function improved. UK experts also agreed that the caregiver burden of AADC deficiency is extremely high. They confirmed that 2.2 caregivers per patient with severe AADC

deficiency was a reasonable estimate and that the caregiver burden would reduce as patient motor function improves.

B.3.15. Interpretation and conclusions of economic evidence

The CEA provided as part of this NICE appraisal confirms that eladocagene exuparvovec is expected to generate transformative, life-extending, and lifelong benefits to patients with AADC deficiency. In the base case, eladocagene exuparvovec is expected to generate [redacted] additional QALYs and [redacted] additional LYs compared to current BSC.

The CEA developed as part of this NICE appraisal is the first and only CEA generated in patients with AADC deficiency. No other CEAs were identified in the SLR conducted for this NICE appraisal other than a published abstract related to this CEA (Simons *et al.* (2022)).[88] The findings from the published abstract were consistent with those in this CEA.

The CEA developed as part of this NICE appraisal is relevant to patients with AADC deficiency who are expected to use the technology in the UK. Eladocagene exuparvovec is expected to be used in the UK in all eligible patients [redacted]. The clinical data informing the CEA are primarily taken from the AADC-010, AADC-011, and AADC-CU/1601 clinical studies in which patients had a mean age of 4 years at baseline and had no motor function.

While it is noted that the eladocagene exuparvovec clinical trials were all conducted in Taiwan in an Asian population, UK experts broadly agreed that race/ethnicity would not impact disease or treatment outcomes. UK experts stated that diagnosis may be earlier in Taiwan due to higher prevalence and noted that patients in Taiwan may have a different mutation to those in the UK. Despite this, UK experts agreed that there is limited evidence of a genotype-phenotype correlation or of the genotype influencing outcomes with eladocagene exuparvovec. In studies for eladocagene exuparvovec, genetic mutation type did not influence outcomes.

In addition to the CEA being relevant to UK patients, it is also reflective of UK clinical management of AADC deficiency. Given the ultra-rare nature of AADC deficiency and therefore limited experience of managing patients in the UK, established patient management in the UK is not clearly defined and patients are managed on an individual basis with symptomatic treatments. UK clinical experts broadly aligned with the CEA inputs related to BSC treatments and visits from a multidisciplinary team of specialists (which were informed by Wassenberg et al 2017 consensus guidelines that had input from Simon Heales, Manju Kurian, and Lisa Flint in the UK). The CEA includes a scenario analysis in which resource use and treatment use inputs are informed by UK clinical expert estimates. The scenario results are similar to the base case, highlighting the applicability of the base case to the UK environment.

While developing a robust model in a disease of such rarity and heterogeneity is extremely challenging, the CEA developed as part of this NICE appraisal has a number of strengths:

- The CEA framework was informed by clinical, patient and HEOR experts over a number of conceptualization stages and took into consideration NICE precedents from similar diseases (e.g. DMD, SMA, MLD). See Section B.3.2.2 for more information.
- The CEA approach used (cohort model based on motor milestone health states) is the optimal approach as it maximises the use of observed clinical trial data and minimizes the uncertainty created by a small sample size. It is less reliant on assumptions and has a lower computational burden than other modelling approaches (e.g. patient-level simulation). See Section B.3.2.2 for more information.
- The CEA is informed by data from patients with up to 9 years of follow-up. This is unprecedented in NICE appraisals for gene therapies and provides confidence in the longer-term outcomes with eladocagene exuparvovec.
- The use of motor milestone health states leverages the primary outcome in trials for eladocagene exuparvovec. Using individual patient PDMS-2 scores to predict motor milestone achievement overcomes issues created by data gaps, differing lengths of follow-up, and heterogeneity in outcome trajectories. Motor milestone achievement is confirmed by clinical experts to be the key outcome in AADC deficiency and improvements in motor function correlate with improvements in other AADC deficiency outcomes (i.e. global symptom improvement). See Section B.3.2.2.6 for more information.
- In the absence of trial EQ-5D or HRQoL data, the model health state utilities are informed by a UK vignette study with TTO elicitation. This is a robust alternative to EQ-5D according to NICE. The health state vignettes are informed by clinical and patient experts and align with the health states in the CEA. See Section B.3.4.5 for more information on utility elicitation.
- The model has been extensively validated and exhaustively researched. Validation has formally involved four clinical expert advisory boards (including one UK validation with the UK's leading AADC deficiency experts) and one HEOR expert advisory board. In addition, elements of the model have been tested with UK statistical experts and HEOR experts with experience representing NICE ERGs and/or developing NICE TSDs.

Despite the steps taken to develop a robust model, the CEA has limitations:

- AADC deficiency is ultra-rare with very limited data in the literature. The model therefore uses data from proxy diseases, including CP, SMA, and MS. The use of proxy diseases was a necessity in most cases given the limited literature. Inputs based on proxy diseases were validated with clinical experts (including in the UK), who confirmed they were appropriate in the absence of AADC deficiency-specific literature.
- Only 28 patients have been treated with eladocagene exuparvovec in the clinical trials informing the CEA. While this represents 10% of all patients with AADC deficiency worldwide, it is a low sample size and means there is high heterogeneity in outcomes

and patient clinical trajectories. In addition, the trials were all conducted in Taiwan meaning the generalizability to the UK population is not fully understood.

- All trials for eladocagene exuparvovec are single-arm, predominantly for ethical reasons given the extremely high unmet need in patients with AADC deficiency. This means that the comparator arm in the model is informed by a NHDB compiled based on a SLR of all unique patients who have ever been described in the literature. To ensure comparability to the trial population, only those patients in the NHDB with poor or no head control by age 2 years were included. Given the limitations in the NHDB, an ITC was not feasible and the CEA is therefore reliant on a naïve comparison.
- The model likely underestimates the severity of AADC deficiency and therefore the potential benefits of eladocagene exuparvovec.

As mentioned above, most of the model limitation are based on the paucity of published data on all aspects of AADC deficiency and the small sample size in the clinical studies. The model may be strengthened in future with longer-term follow-up from the clinical studies coupled with evidence collected as part of the AADCAware registry. Notably, the AADCAware registry will collect natural history data as well as data in patients treated with eladocagene exuparvovec. With AADCAware, PTC Therapeutics is committed to collecting at least 10 years of follow-up data from patients treated with AADC deficiency, including those treated in the UK and other European populations. In turn PTC is committed to improving the lives of patient and families who suffer from AADC deficiency, who currently have little hope of positive outcomes with current BSC.

B.3.16. Cost to the NHS and Personal Social Services

The BIA analysis is developed as part of the NICE appraisal and is aligned with the CEA, using the same clinical and economic evidence. The proportion of patients in each motor milestone health state over the 5 years of the BIA is taken directly from the CEA and is used to calculate the treatment acquisition, administration, and resource use costs. The following section describes in detail the analysis carried out in order to perform the budget impact test.

Due to the rarity of AADC deficiency, there is very limited epidemiology data for the condition. Therefore, epidemiology data are based on estimations by UK AADC deficiency clinical experts[5]. UK clinical experts estimate [redacted] eligible for eladocagene exuparvovec in England and Wales currently and each year over the next five years there will be [redacted]. Table 78 presents the eligible population over the next 5 years.

Table 78: Eligible patients for eladocagene exuparvovec over the next five years in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients eligible for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact model considers two scenarios, a market without eladocagene exuparvovec (current management) and a market with eladocagene exuparvovec (proposed management). Table 79 presents the proposed market share figures over 5 years.

Table 79: Market uptake and market share of the eligible population under current and proposed AADC deficiency management

Comparator	Year				
	2022	2023	2024	2025	2026
Current management					
Eladocagene exuparvovec + BSC	0%	0%	0%	0%	0%
BSC only	100%	100%	100%	100%	100%
Proposed management					
Eladocagene exuparvovec + BSC	100%	100%	100%	100%	100%
BSC only	0%	0%	0%	0%	0%

Abbreviations: AADC – aromatic L-amino acid decarboxylase; BSC – best supportive care.

The model considers treatment acquisition and administration costs, as well as resource use and adverse event costs. Eladocagene exuparvovec has a substantial one-off unit cost of £[redacted], in addition to administration and pre-/post-operative costs of £[redacted]. BSC treatment and resource use is extensive, involving a wide range of symptomatic therapies, follow-up visits, hospitalisation, and medical and technical procedures required to manage a patient with AADC deficiency. In the BIM, the total BSC resource use and treatment costs vary by motor milestone achievement, with lower motor milestones associated with higher costs. The yearly disease BSC costs associated with patients with no-motor function or full-head control is £15,634, compared to £8,693 in patients able to stand with support or walk with assistance.

Eladocagene exuparvovec substantially improves achievement of motor milestones versus BSC. By improving motor milestones and patient outcomes, the introduction of eladocagene exuparvovec to the NHS is expected to reduce resource use to the NHS and translate into resource use cost savings of £1,652 in year 1, £4,332 in year 2, £7,061 in year 3, £6,897 in year 4, and £6,329 in year 5. The cost-savings are primarily driven by a reduction in the frequency of specialist visits. The potential benefits provided by eladocagene exuparvovec are sustained over the 5-year period of the BIM and are expected to continue throughout a patient's lifetime.

Eladocagene exuparvovec is associated with a manageable and very predictable budget impact in the UK. At list price, introducing eladocagene exuparvovec to the NHS is expected to lead to a budget impact of £[redacted], £[redacted], £[redacted], £[redacted] and £[redacted] in years one to five, respectively (Table 80). Eladocagene exuparvovec therefore very comfortably passes the NICE budget impact test (budget impact must not exceed £20 million in any of the first 3 years).[133] At the PAS price, eladocagene exuparvovec is even more affordable, associated with a manageable average budget impact per year of £[redacted] and a cumulative total budget of £[redacted] (Table 81).

The full breakdown of costs for current management (without eladocagene exuparvovec) and proposed management (with eladocagene exuparvovec) are presented in and Table 82 and Table 83, respectively. In summary:

- As expected, treatment acquisition costs increase substantially due to the introduction of eladocagene exuparvovec. In year one, the treatment acquisition cost with current management is £3,151, compared to £[redacted] following introduction of eladocagene exuparvovec. In year five, the treatment acquisition cost with current management is £8,950, increasing to £[redacted] following £introduction of eladocagene exuparvovec.
- As a result of the clinical efficacy of eladocagene exuparvovec and improved motor function for patients treated with the gene-replacement therapy, the cost of resource use by year five decreases from £43,704 with current management to £37,375 with eladocagene exuparvovec.
- As adverse events are only applied to the first year after treatment with eladocagene exuparvovec, the costs remain at £2,305 throughout years one to five in proposed management.

Figure 57: Base-case budget impact of introducing eladocagene exuparvovec in England and Wales

[redacted]

Table 80: Budget impact of introducing eladocagene exuparvovec in England and Wales (list price)

Year	Current management	Following introduction of eladocagene exuparvovec	Budget Impact
1	£[redacted]	£[redacted]	£[redacted]
2	£[redacted]	£[redacted]	£[redacted]
3	£[redacted]	£[redacted]	£[redacted]
4	£[redacted]	£[redacted]	£[redacted]
5	£[redacted]	£[redacted]	£[redacted]
Average (5 years)	£[redacted]	£[redacted]	£[redacted]
Total (5 years)	£[redacted]	£[redacted]	£[redacted]

Table 81: Budget impact of introducing eladocagene exuparvovec in England and Wales (PAS price)

Year	Current management	Following introduction of eladocagene exuparvovec	Budget Impact
1	£[redacted]	£[redacted]	£[redacted]
2	£[redacted]	£[redacted]	£[redacted]
3	£[redacted]	£[redacted]	£[redacted]
4	£[redacted]	£[redacted]	£[redacted]
5	£[redacted]	£[redacted]	£[redacted]
Average (5 years)	£[redacted]	£[redacted]	£[redacted]
Total (5 years)	£[redacted]	£[redacted]	£[redacted]

Abbreviations: PAS – patient access scheme

Table 82: Breakdown of costs with current management (i.e. without eladocagene exuparvovec)

Year	Treatment acquisition	Treatment administration	Resource use	Adverse events
1	£[redacted]	[redacted]	£[redacted]	[redacted]
2	£[redacted]	[redacted]	£[redacted]	[redacted]
3	£[redacted]	[redacted]	£[redacted]	[redacted]
4	£[redacted]	[redacted]	£[redacted]	[redacted]
5	£[redacted]	[redacted]	£[redacted]	[redacted]
Average	£[redacted]	[redacted]	£[redacted]	[redacted]

Table 83: Breakdown of costs with proposed management (i.e. with eladocagene exuparvovec; list price)

Year	Treatment acquisition	Treatment administration	Resource use	Adverse events
1	£[redacted]	£[redacted]	£[redacted]	£[redacted]
2	£[redacted]	£[redacted]	£[redacted]	£[redacted]
3	£[redacted]	£[redacted]	£[redacted]	£[redacted]
4	£[redacted]	£[redacted]	£[redacted]	£[redacted]
5	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Average	£[redacted]	£[redacted]	£[redacted]	£[redacted]

Table 84: Breakdown of costs with proposed management (i.e. with eladocagene exuparvovec; PAS price)

Year	Treatment acquisition	Treatment administration	Resource use	Adverse events
1	£[redacted]	£[redacted]	£[redacted]	£[redacted]
2	£[redacted]	£[redacted]	£[redacted]	£[redacted]
3	£[redacted]	£[redacted]	£[redacted]	£[redacted]
4	£[redacted]	£[redacted]	£[redacted]	£[redacted]
5	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Average	£[redacted]	£[redacted]	£[redacted]	£[redacted]

Abbreviations: PAS – patient accesss scheme

The limitations associated with this BIM are mostly related to the ultra-rare nature of AADC deficiency, which means that limited data are available to support model inputs and assumptions.

The lack of available literature, rarity, and challenges of diagnosing make it difficult to estimate the eligible patient population in the UK. As expected given the high initial acquisition cost of eladocagene exuparvovec, the number of prevalent and incident patients has a considerable bearing on the overall budget impact. The population used in this BIM is based on the opinion and insights of UK clinician experts who directly manage patients with AADC deficiency.[5]

The ultra-rare and severe nature of AADC deficiency also means that it is difficult to conduct clinical trials in large populations, as was the case with eladocagene exuparvovec trials. The small sample size in clinical trials for the gene-replacement therapy resulted in heterogeneity in clinical outcomes, making the efficacy outcomes in the model uncertain.

Furthermore, the rarity of AADC deficiency means there are data gaps in the literature on key clinical inputs. In the absence of head-to-head trial evidence, a NHDB was used to populate the BSC effectiveness in terms of motor milestone achievement. The NHDB was applied in the BIM through a naïve comparison because an indirect comparison was not feasible. Despite this, the NHDB is the most comprehensive and detailed source of data available that describes the management of patients with severe AADC deficiency receiving BSC. Further details on methods and justification for the NHDB are presented in Section B.2.9 and Appendix D.1.8.

In addition to uncertainty in the clinical outcomes, established treatment use and resource use in AADC deficiency is highly variable and patient-specific, meaning that the estimates of BSC treatment and resource use in the model are uncertain.

In summary, eladocagene exuparvovec is the first and only disease-modifying therapy for the treatment with AADC deficiency. As a gene-replacement therapy, it has a high acquisition cost but provides lifelong benefits that may not be realised in a five-year budget impact model. Given the very low number of prevalent and incident patients in the UK, eladocagene exuparvovec is associated with a manageable and predictable budget impact that is

comfortably within the NICE budget impact test.[133] As expected for a highly innovative gene-replacement therapy for an ultra-rare condition, the budget impact is driven by the high upfront treatment acquisition cost of eladocagene exuparvovec versus BSC.

B.4. References

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Please see the Draft Upstaza SmPC in the PDF reference pack provided.[14]

C1.1 SmPC

The published SmPC can be found in the reference pack.[14]

C1.2 UK public assessment report

The UK public assessment report is not yet available.

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

D1.1.1 Search strategy

Pre-defined, NICE-compliant, study design filters were used to identify evidence for all review questions. The searches included terms for free text and keywords (Medical Subject Heading (MeSH) and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review question. Date restrictions were not applied to the searches, but a language restriction was applied such that only publications reporting in English were accepted.

Searches were conducted in the following databases to identify evidence for all review questions, clinical publications, economic and HRQoL publications:

- Embase (covers biomedical literature from 1974 to present)
- MEDLINE (covers journals from 1966 to present)
- Embase Classic (the Embase back file covering citations between 1947-1973)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)
- Cochrane Clinical Answers
- CRD HTA Database
- CRD NHS EED (from 1994 and March 2015)
- ScHARRHUD (from 2010 to present)
- EuroQol database

Supplementary searches of “grey” literature were performed using set search terms in:

- Google Scholar
- NICE website
- PBAC website
- CADTH website
- SMC website
- ICER website

Furthermore, searches included clinicaltrials.gov, the manufacturer’s repository of evidence, websites of manufacturers of comparator products, and bibliographic searching of any SLRs identified during screening. The following relevant congresses were also searched with a date restriction, where possible, over the last three years:

- ISPOR conference proceedings (EU)
- ISPOR conference proceedings (US)
- European Paediatric Neurology Society
- Society for the Study of Inborn Errors of Metabolism
- International Congress of Inborn Errors of Metabolism
- British Paediatric Neurology Association.
- World Orphan Drug Congress
- European Society for Gene and Cell Therapy
- American Society of Gene and Cell Therapy
- Gene Therapy for Neurological Disorders (US/EU).

Table 85, Table 86, Table 87, Table 88 and Table 89 present the search strategies for Embase, MEDLINE and Embase Classic; CENTRAL and Cochrane Clinical Answers; CRD HTA Database; CRD NHS EED; ScHARRHUD; and EuroQol database.

The strategies described in this section, in line with NICE guidance, apply to retrieval of both published and unpublished evidence.

Table 85: Embase, MEDLINE and Embase Classic (Embase index terms used as all databases were searched within the Embase interface) [date searched: 11th November 2021]

Clinical search strategy		
Description	Search terms	Hits
Population	'aromatic amino acid decarboxylase deficiency'/exp OR 'aadc gene' OR 'AADC-d' OR 'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR 'aadc-d' OR 'dopa decarboxylase deficiency' OR 'ddc gene' OR 'ddc deficiency' OR 'aadc-d' OR 'aadc varian*' OR 'aadc syndrom*' OR 'aadc disease' OR 'aadc disorder'	551
Interventions/ comparators	'Upstaza' OR 'AAV2 NEAR/2 hAADC' OR 'adeno-associated virus adj8 human AADC' OR 'eladocagene exuparvovec' OR 'AGIL NEAR/2 AADC'	50
Study types: RCT Filter	('clinical trial'/de OR 'randomised controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomisation'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	2,480,623
Observation study filter	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomised controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow-up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross-sectional' NEXT/1 (study OR studies)):ti,ab)	3,941,832
Combine filters and restrict date	#1 OR #2 AND (#3 OR #4) AND [humans]/lim	113
Cost-effectiveness, HRQoL, and cost and resource use studies search strategy		
Economic Filter	'socioeconomics'/de OR 'cost-benefit analysis'/de OR 'cost-effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost-utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimisation analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,037,062

Cost-effectiveness, HRQoL, and cost and resource use studies search strategy		
Quality-of-life filter[134] (https://abstracts.cochrane.org/2015-vienna/ sensitivity-search-filter-designed-identify-studies-reporting-health-state-utility)	'quality-adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality-adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health-state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR EQ-5D OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR (caregiver OR carer)	1,194,398
Resource use filter	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalisation'/de OR hospitalisation*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalised:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti) OR (carer OR carers OR caregiver OR caregivers)	2,041,276
Combine terms and restrict date	#1 AND (#6 OR #7 OR #8) AND [humans]/lim	35
Combine terms	#5 OR #9	142

Abbreviations: HRQoL – Health-related quality-of-life; RCT – Randomised control trial;

Table 86: CENTRAL and Cochrane Clinical Answers (Cochrane Library interface) [date searched: 11th November 2021]

Clinical search strategy		
Description	**Search terms**	**Hits**

Clinical search strategy		
Terms for population	"aromatic amino acid decarboxylase deficiency" OR "aadc gene" OR "AADC-d" OR "aromatic amino acid decarboxylase deficiency" OR "aromatic L-amino acid decarboxylase deficiency" OR "aadc-d" OR "dopa decarboxylase deficiency" OR "ddc gene" OR "ddc deficiency" OR "aadc-dAADC deficiency"	2
MeSH terms for population	MeSH descriptor [aromatic L-amino acid decarboxylase] explode all trees	11
Interventions/comparators	“Upstaza” OR “AAV2” NEAR/2 “hAADC” OR “adeno-associated virus” adj8 “human AADC” OR “eladocagene exuparvovec” OR “AGIL” NEAR/2 “AADC”	0
Combine terms	#1 OR #2 OR #3 in trials	12

Abbreviations: MeSH – Medical subject heading

Table 87: ScHARRHUD search strategy [date searched: 11th November 2021]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc d’ OR ‘AADC-d’	0

Abbreviations: ; HRQoL – Health-related quality-of-life; ScHARRHUD - School of health and related research, University of Sheffield

Table 88: EuroQoL database search strategy [date searched: 11th November 2021]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc d’ OR ‘AADC-d’	0

Abbreviations: HRQoL – Health-related quality-of-life

Table 89: NHS HTA and EED search strategy (via University of York website) [date searched: 11th November 2021]

CRD HTA and EED database - Cost-effectiveness, cost and resource use and quality-of-life search strategy		
Description	**Search terms**	**Hits**
Terms for population	aromatic amino acid decarboxylase deficiency OR aromatic L-amino acid decarboxylase deficiency OR aadc-d OR aadc-d OR AADC-d	0
Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	25,686
Combine filters	#1 AND #2 in NHSEED, HTA	0
QoL filter	qol OR quality-of-life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	13,073
Combine terms	#1 AND #4 in NHSEED, HTA	0

Abbreviations: CRD – Centre for reviews and dissemination; EED – Economic evaluation database; HTA – Health technology assessment; NHS – National health service; QoL – Quality-of-life

D1.1.2 Study selection

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified publications based on title and abstract (first pass) for inclusion using the review question and selection criteria. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in line with NICE guidelines.

Following the completion of first pass, full text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria by two independent reviewers. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in alignment with NICE guidance.

D1.1.3 Data extraction

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers or by consulting a third reviewer if necessary. For each publication, data were extracted into a data collection form (Excel based with tables suitably formatted to align with NICE 2022 SLR template) and developed in line with the University of York CRD and NICE reporting requirements [135,136].

No RCTs were identified within this SLR, however, should any RCTs have been identified in the clinical section of the SLR, a comprehensive quality assessment using NICE guidelines would have been conducted. This assessment is based on the following questions [135,136]:

- Was the method used to generate random allocations adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors, e.g., severity of disease?
- Was the treatment allocation sequence adequately concealed?
- Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data.

- In line with NICE guidance for HST appraisals, non-RCTs were quality assessed according to CRD guidance [135]. Each non-RCT study identified in the clinical SLR underwent a comprehensive quality assessment using Critical Appraisal Skills Programme as per NICE HST guidelines. The assessment consisted of the following questions:
- Was the cohort recruited in an acceptable way?
- Was the exposure accurately measured to minimise bias?
- Was the outcome accurately measured to minimise bias?
- Have the authors identified all important confounding factors?
- Have the authors taken account of confounding factors in the design and/or analysis?
- Was the follow-up of patients complete?
- How precise (e.g., in terms of confidence interval and p-values) are the results?

If any cost-effectiveness publications were found, a quality assessment of these cost-effectiveness publications would have been conducted using the Drummond and Jefferson criteria [137].

D1.1.4 Study, intervention, and patient characteristics

The following study characteristics were extracted in the SLR:

- Study name
- Study year
- Study author
- Study design (e.g., RCT, non-randomised clinical trial, observational study, number of arms, double blind, open label etc.)
- Study intervention(s)
- Study endpoints
- Study duration and follow-up period
- Outcomes reported
- Sample size

Intervention characteristics

- Treatment regimen
- Treatment dose
- Method of administration
- Frequency of administration
- Duration of treatment

Patient characteristics

- Age at baseline
- Age at diagnosis
- Gender
- Race and ethnicity
- Genotype
- PDMS-2 total score at baseline
- AIMS total score at baseline
- Baseline height
- Baseline weight

D1.1.5 Study quality

Due to the ultra-rare nature of AADC deficiency and therefore limited patient population, as well as ethical considerations, all the clinical trials identified and used in this appraisal were non-RCTs and single-arm in design. Consequently, only the assessment criteria for non-RCT trials were applied.

In line with NICE guidance for HST appraisals, non-RCTs were quality assessed according to CRD guidance. Each non-RCT study identified in the clinical SLR underwent a comprehensive quality assessment using Critical Appraisal Skills Programme as per NICE HST guidelines. The assessment consisted of the following questions:

- Was the cohort recruited in an acceptable way?
- Was the exposure accurately measured to minimise bias?
- Was the outcome accurately measured to minimise bias?
- Have the authors identified all important confounding factors?
- Have the authors taken account of confounding factors in the design and/or analysis?
- Was the follow-up of patients complete?
- How precise (e.g., in terms of confidence interval and p-values) are the results?

If any cost-effectiveness publications were found, a quality assessment of these cost-effectiveness publications would have been conducted using the Drummond and Jefferson criteria. [137]

D1.1.6 Selection criteria

The selection criteria specified in Table 90, Table 91, Table 92 and Table 93 were used to inform the inclusion of publications at first and second pass stages of the reviews. Publications published as abstracts, conference presentations or press releases were eligible if adequate data are provided in line with the inclusion criteria. These criteria apply to both published and unpublished studies.

Table 90: Selection criteria for RCTs and non-RCTs studies

Inclusion criteria	
Population	Patients with AADC deficiency
Interventions/ comparators	Any of the following interventions used in the treatment of AADC deficiency: • Upstaza® (eladocagene exuparvovec, PTC-AADC, or any mention of a gene therapy to restore AADC via viral vectors, e.g., AAV2-hAADC) • MAO inhibitors • Dopamine agonists • Vitamin B6 (pyridoxine) • Anticholinergic agents • Benzodiazepines • Alpha-adrenoceptor agonists • Levodopa • Melatonin
Outcomes	• Functionality of the DDC gene (i.e. production and level of the AADC enzyme) • Dopamine levels • Serotonin levels • Motor functioning (including age-appropriate motor milestones such as sitting, standing and walking) via any of the following assessments: • PDMS-2 • AIMS • Bayley-III totals and subscales • CDIIT • Autonomic nervous system functioning • Speech and language development • Cognitive development • Sleep • Neurotransmitter metabolite HVA in CSF • Neurotransmitter metabolite 5-HIAA levels in CSF • Putaminal signal of 6-[18F] flurodopa-PET • Body weight

	• Neurological examination findings with respect to muscle tone (i.e., floppiness), • OGC episodes • Dystonia • Muscle power • Deep tendon reflex response • Mortality • AEs
Study design	• RCTs • Non-RCTs • Observational studies (incl registries) • Cross-sectional studies • Case series
Language restrictions	English
Search dates	Unrestricted
Exclusion criteria	
Population	• Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions	Unrestricted
Outcomes	• No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes
Study design	• Animal studies • In vitro/ex vivo studies • Individual case study reports
Language restrictions	Non-English
Search dates	Unrestricted

Abbreviations: AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AE – Adverse event; AIMS – Alberta Infant Motor Scale; Bayley-III – Bayley Scales of Infant Development 3rd edition; CDIIT – Comprehensive Developmental Inventory for Infants and Toddlers; CSF – Cerebrospinal fluid; DDC – Dopa decarboxylase; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; MAO – Monoamine oxidase; N/A – Not applicable; OGC – Oculogyric crises; PDMS-2 – Peabody Developmental Motor Scale 2nd edition; PET – Positron emission tomography; RCT – Randomised controlled trials

Table 91: Selection criteria for cost-effectiveness studies

Inclusion criteria	
Population	Patients with AADC deficiency
Interventions/ comparators	• Any intervention/comparator (i.e. no restriction)
Outcomes	• Cost per QALY gained • Cost per life year gained
Study design	• Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • EEACT
Language restrictions	English
Publication type	• Article, conference abstract, conference paper, article in press
Exclusion criteria	
Population	• Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions	• No intervention / comparators of interest
Outcomes	• No reported outcomes of interest, i.e., budget impact model outcomes
Study design	• Burden of disease study • Resource use study • Budget impact study
Language restrictions	Non-English
Publication type	• Short survey • Reviews • Letters • Comment articles

Abbreviations: AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; EEACT – Economic evaluation alongside clinical trials; QALY – Quality-adjusted life year; SLR – Systematic literature review

Table 92: Selection criteria for HRQoL studies

Inclusion criteria	
Population	• Patients with AADC deficiency • Caregivers of patients with AADC deficiency
Interventions/ comparators	Any intervention/comparator (i.e. no restriction)
Outcomes	• Utilities • Disutilities • HRQoL measures (i.e. no restriction)
Study design	• RCTs • Non-RCTs • Observational studies • HRQoL elicitation studies • HRQoL validation studies • Economic evaluations: • Cost-utility analysis • EEACT
Language restrictions	English
Publication type	• Article, conference abstract, conference paper, article in press
Exclusion criteria	
Population	• Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions	• No intervention / comparators of interest
Outcomes	• No reported outcomes of interest, i.e., budget impact model outcomes
Study design	• Individual case study reports

Language restrictions	Non-English
Publication type	• Short survey • Reviews • Letters • Comment articles

Abbreviations: AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; EEACT – Economic evaluation alongside clinical trials; HRQoL – Health-related quality-of-life; RCT – Randomised controlled trials; SLR – Systematic literature review

Table 93: Selection criteria for cost and resource use studies

Inclusion criteria	
Population	• Patients with AADC deficiency • Caregivers of patients with AADC deficiency
Interventions/comparators	Any intervention/comparator (i.e. no restriction)
Outcomes	• Unit costs • Resource use • Budget impact • Cost of illness
Study design	• Cost study • Burden of disease study • Resource use study • Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • WTP studies • EEACT
Language restrictions	English
Publication type	Article, conference abstract, conference paper, article in press

Exclusion criteria	
Population	Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions	No intervention / comparators of interest
Outcomes	No reported outcomes of interest, i.e., budget impact model outcomes
Study design	Individual case study reports
Language restrictions	Non-English
Publication type	• Short survey • Reviews • Letters • Comment articles

Abbreviations: AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; EEACT – Economic evaluation alongside clinical trials; QALY – Quality-adjusted life year; SLR – Systematic literature review; WTP – Willingness to pay

Table 94: Excluded studies at second pass and rationale (n=15)

Primary study reference	Study title	Reason for exclusion
Asari *et al*. 2019	FMT-PET analysis in gene therapy for AADC-d	Outcomes
Buesch *et al.* 2021	PRO48 Utilities in a rare disease collected via vignettes in general population samples from the UK and France: comparison of Results	Outcomes
Buesch *et al.* 2021	PRO51 Caring for an Individual with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Analysis of Reported Time for Practical and Emotional Care and Paid/Unpaid Help	Outcomes
Christine *et al.* 2022	Safety of AADC Gene Therapy for Moderately Advanced Parkinson Disease: Three-Year Outcomes from the PD-1101 Trial	Population
Factor *et al.* 2021	The PD-1102 trial in advanced Parkinson's disease: Safety and clinical outcomes from a 3-year phase 1b study of AADC gene therapy administered via a posterior approach	Population
Hovarth *et al.* 2012	Recurrent rhabdomyolysis in a girl with a severe course of AADC-d	Population

Hwu *et al.* 2021	Gene Therapy with Eladocagene Exuparvovec Improves Cognition and Language in Patients with Aromatic L-amino Acid Decarboxylase Deficiency	Outcomes
Le Dissez *et al.* 2021	PRO28 Healthcare Resource Use (HCRU) of Patients with Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D) in France	Outcomes
Le Dissez *et al.* 2021	PRO2 Burden of Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D) in France with a FOCUS on Patient Symptoms and Motor Milestones Development	Outcomes
Pearson *et al.* 2020	AADC-d from infancy to adulthood: Symptoms and developmental outcome in an international cohort of 63 patients	Outcomes
Skrobanski *et al*. 2021	The impact of caring for an individual with aromatic L-amino acid decarboxylase (AADC) deficiency: a qualitative study and the development of a conceptual model	Outcomes
Smith *et al.* 2019	Engaging with parents, caregivers, and clinicians to capture the health-related quality-of-life of children living with AADC-d for a vignette and discrete choice experiment study	Outcomes
Smith *et al*. 2020	PRO133 Validating Vignettes for a Rare Disease Using Clinician Interviews to Evaluate the Impact on Health-Related Quality-of-life in Aromatic L-amino Acid Decarboxylase (AADC) Deficiency in France	Outcomes
Smith *et al.* 2020	PRO118 Deriving Vignettes for a Rare Disease Using Parent, Caregiver and Clinician Interviews to Evaluate the Impact on Health-Related Quality-of-life	Outcomes
Sudhapalli *et al*. 2020	PRO10 Identifying Appropriate PROXY Diseases for Estimating LONG-TERM Survival and IMPACT on Health-Related Quality-of-life of Patients with Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D)	Outcomes

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; AADC-d – Aromatic L-amino acid decarboxylase deficiency; HCRU – Healthcare resource use; FMT - Fluorescence molecular tomography; PET – Positron emission tomography

Table 95: Publications excluded at first pass (n=103)

Publication Year	Author	Title
2021	Ling T.-K., Wong K.-C., Chan C.Y., Lau N.K.-C., Law C.-Y., Lee H.-C.H., Lai C.-K., Chong Y.-K., Yau K.-C.E., Cheung K.-M., Ko C.-H., Fung C.-W., Lee L.-K., Wong S.S.-N., Mak C.M., Chan A.Y.-W., Tam S., Lam C.-W.	Urine organic acid as the first clue towards aromatic L-amino acid decarboxylase (AADC) deficiency in a high prevalence area
2021	Chien Y., Hwu P., Lee N., Tseng S., Wang A., Schilling T., Wang J., Kristensen A., Ozdas S., Tai C.	Reductions in Oculogyric Crisis Duration and Frequency in Children with Aromatic L-amino Acid Decarboxylase Deficiency Treated with Eladocagene Exuparvovec Gene Therapy: Results from 3 Clinical Trials
2021	Hwu P., Chien Y., Lee N., Tseng S., Wang A., Wang J., Schilling T., Ozdas S., Tai C.	Eladocagene Exuparvovec Improves Body Weight and Reduces Respiratory Infections in Patients with Aromatic L-amino Acid Decarboxylase Deficiency
2021	Wassenberg T., Geurtz B.P.H., Monnens L., Wevers R.A., Willemsen M.A., Verbeek M.M.	Blood, urine and cerebrospinal fluid analysis in TH and AADC deficiency and the effect of treatment
2021	Gowda V.K., Vegda H., Nagarajan B.B., Shivappa S.K.	Clinical Profile and Outcome of Indian Children with Aromatic L-amino Acid Decarboxylase Deficiency: A primary CSF Neurotransmitter Disorder Mimicking as Dyskinetic Cerebral Palsy
2021	Burlina A., Giuliani A., Polo G., Gueraldi D., Gragnaniello V., Cazzorla C., Opladen T., Hoffmann G., Blau N., Burlina A.P.	Detection of 3-O-methyldopa in dried blood spots for neonatal diagnosis of aromatic L-amino-acid decarboxylase deficiency: The north-eastern Italian experience
2021	Hwu P.W.-L., Chien Y.-H., Lee N.-C., Tseng S.-H., Pykett M., Tai C.-H.	Improved motor function in children with aromatic L-amino acid decarboxylase (AADC) deficiency treated with eladocagene exuparvovec (PTC-AADC): Interim Findings from a Phase 1/2 Study
2021	Chien Y.-H., Hwu P.W.-L., Lee N.-C., Tseng S.-H., Pykett M., Tai C.-H.	Improved motor function in children with aromatic L-amino acid decarboxylase (AADC) deficiency treated with eladocagene exuparvovec (PTC-AADC): Interim findings from a phase 2 trial
2021	Hwu P.W.-L., Chien Y.-H., Lee N.-C., Tseng S.-H., Pykett M., Tai C.-H.	Improved motor function in children with aromatic L-amino acid decarboxylase (AADC) deficiency treated with eladocagene exuparvovec (PTC-AADC): Compassionate use study
2021	Tristán-Noguero A., Borràs E., Molero-Luis M., Wassenberg T., Peters T., Verbeek M.M., Willemsen M., Opladen T., Jeltsch K., Pons R., Thony B., Horvath G., Yapici Z., Friedman J., Hyland K., Agosta G.E., López-Laso E., Artuch R., Sabidó E., García-Cazorla À.	Novel Protein Biomarkers of Monoamine Metabolism Defects Correlate with Disease Severity
2021	Kuseyri Hübschmann O., Mohr A., Friedman J., Manti F., Horvath G., Cortès-Saladelafont E., Mercimek-Andrews S., Yildiz Y., Pons R., Kulhánek J., Oppebøen M., Koht J.A., Podzamczer-Valls I., Domingo-Jimenez R., Ibáñez S., Alcoverro-Fortuny O., Gómez-Alemany T., de Castro P., Alfonsi C., Zafeiriou D.I., López-Laso E., Guder P., Santer R.,	Brain MR patterns in inherited disorders of monoamine neurotransmitters: An analysis of 70 patients

Publication Year	Author	Title
	Honzík T., Hoffmann G.F., Garbade S.F., Sivri H.S., Leuzzi V., Jeltsch K., García-Cazorla A., Opladen T., Harting I.	
2021	Havalı C., Dorum S., Ekici A., Görükmez Ö.	Approaches for diagnosis and treatment in neurotransmitter disorders of childhood
2021	Böhnke A., Minartz C., Radeck-Knorre S., Schwenke C., Neubauer A.S.	Gene therapy for rare diseases: Differences to chronic therapy and example AADC-d
2020	Senek M., Nyholm D., Nielsen E.I.	Population pharmacokinetics of levodopa gel infusion in Parkinson's disease: effects of entacapone infusion and genetic polymorphism
2020	Peters T.M.A., Engelke U.F.H., de Boer S., van der Heeft E., Pritsch C., Kulkarni P., Wevers R.A., Willemsen M.A.A.P., Verbeek M.M., Coene K.L.M.	Confirmation of neurometabolic diagnoses using age-dependent cerebrospinal fluid metabolomic profiles
2020	Brennenstuhl H., Garbade S.F., Okun J.G., Feyh P., Hoffmann G.F., Langhans C.-D., Opladen T.	Semi-quantitative detection of a vanillactic acid/vanillylmandelic acid ratio in urine is a reliable diagnostic marker for aromatic L-amino acid decarboxylase deficiency
2020	Chen Y., Ou R., Zhang L., Gu X., Yuan X., Wei Q.-Q., Cao B., Zhao B., Wu Y., Shang H.	Contribution of five functional loci of dopamine metabolism-related genes to Parkinson’s disease and multiple system atrophy in a Chinese population
2020	Factor S., Van Laar A., Richardson R., Christine C., Larson P., Kostyk S., Lonser R., Li C., Liang G., Meier A., Fine E., Gross R.	AADC gene therapy administered via a posterior approach: 18-month results from the PD-1102 trial in advanced Parkinson's disease
2020	Christine C., Richardson R., Van Laar A., Thompson M., Herbert K., Li C., Liang G., Fine E., Larson P.	Three-year safety and clinical outcomes from the PD-1101 trial of AADC gene therapy for advanced Parkinson's disease
2020	Bhoj E.J., Rajabi F., Baker S.W., Santani A., Tan W.-H.	Imprinted genes in clinical exome sequencing: Review of 538 cases and exploration of mouse-human conservation in the identification of novel human disease loci
2020	Nutt J.G., Curtze C., Hiller A., Anderson S., Larson P.S., Van Laar A.D., Richardson R.M., Thompson M.E., Sedkov A., Leinonen M., Ravina B., Bankiewicz K.S., Christine C.W.	Aromatic L-amino Acid Decarboxylase Gene Therapy Enhances Levodopa Response in Parkinson's Disease
2020	Hyland K., Reott M.	Prevalence of Aromatic L-amino Acid Decarboxylase Deficiency in At-Risk Populations
2019	Wang Y., Ke Z., Zou H., Lin M., Qiu M., Gu W., Chen Y.	Clinical and genetic analysis of two pedigrees affected with aromatic L-amino acid decarboxylase deficiency

Publication Year	Author	Title
2019	Van Laar A., Richardson R., Sedkov A., Fine E., Bankiewicz K., Ravina B., Larson P., Christine C.	Longitudinal analysis of the modified Hoehn and Yahr disease stage in PD-1101, a Phase 1b clinical study of VY-AADC01
2019	Gilbert L., Black K., Opladen T., Jeltsch K., Garcia-Cazorla A., Leuzzi V., Tay S., Sykut-Cegielska J., Andrews S., Kato M., Luecke T., Oppeboen M., Kurian M., Flint L., Pearson T.	The natural history of AADC deficiency: A retrospective study
2019	Hitti F.L., Yang A.I., Gonzalez-Alegre P., Baltuch G.H.	Human gene therapy approaches for the treatment of Parkinson's disease: An overview of current and completed clinical trials
2019	Segantini T.G., Spini G.R., Gianchini-Segantini T., Carneiro Z.A., Vagnini L., Fonseca J.H.R., Franco J.F.S., Lourenco C.M.	Unravelling AADC Deficiency: Natural History in a Brazilian Cohort of Patients
2019	Fola F., Spini G.R., Segantini T.G., Fonseca J.H.R., Vagnini L., Franco J.F.S., Carneiro Z.A., Lourenco C.M.	"going backwards to diagnosis forward": Overcoming barriers in the diagnosis of AADC deficiency in Latin America
2019	Larson P.S., Christine C., Richardson M., Van Laar A., Kells A., Ravina B., Thompson M., Martin A., Bankiewicz K.	Long-term AADC activity following administration of VY-AADC01 gene therapy using novel intraoperative MRI-monitored intraparenchymal delivery
2019	Christine C.W., Bankiewicz K.S., Van Laar A.D., Richardson R.M., Ravina B., Kells A.P., Boot B., Martin A.J., Nutt J., Thompson M.E., Larson P.S.	Magnetic resonance imaging–guided phase 1 trial of putaminal AADC gene therapy for Parkinson's disease
2019	Genario R., Giacomini A.C.V.V., Demin K.A., dos Santos B.E., Marchiori N.I., Volgin A.D., Bashirzade A., Amstislavskaya T.G., de Abreu M.S., Kalueff A.V.	The evolutionarily conserved role of melatonin in CNS disorders and behavioural regulation: Translational lessons from zebrafish
2019	Christine C.W., Larson P.S., Van Laar A., Richardson R.M., Ravina B., Kells A., Martin A.J., Thompson M.E., Bankiewicz K.S.	Safety and efficacy of VY-AADC01 for medication refractory Parkinson's disease in an on-going phase 1b study
2018	Nutt J., Curtze C., Christine C.W., Larson P.S., Laar A.V., Richardson R.M., Boot B., Thompson M.E., Sedkov A., Leinonen M., De Somer M., Bankiewicz K.S., Ravina B.	AADC gene therapy (VY-AADC01) enhances responses to iv-levodopa in Parkinson's disease (PD)
2018	Zadel M., Maver A., Kovanda A., Peterlin B.	DNA methylation profiles in whole blood of Huntington's disease patients
2018	Portaro S., Gugliandolo A., Scionti D., Cammaroto S., Morabito R., Leonardi S., Fraggetta F., Bramanti P., Mazzon E.	When dysphoria is not a primary mental state
2018	Ravina B., Christine C.W., Larson P.S., Van Laar A., Richardson R.M., Kells A., Boot B., Martin A., Thompson M., Bankiewicz K.S.	AADC gene therapy for advanced Parkinson's disease: Interim results of a phase 1b trial

Publication Year	Author	Title
2018	Hyland K., Reott M.	Prevalence of aromatic L-amino acid decarboxylase deficiency in at-risk populations
2018	Chien Y.-H., Lee N.-C., Tseng S.-H., Tai C.-H., Conway A.M., Gruis K., Pykett M., Hwu W.-L.	Gene therapy in children with AADC deficiency with AGIL-AADC leads to de novo dopamine production and sustained improvement in motor milestones over 5 years
2018	Kuster A., Arnoux J.-B., Barth M., Lamireau D., Houcinat N., Goizet C., Doray B., Gobin S., Schiff M., Cano A., Amsallem D., Barnerias C., Chaumette B., Plaze M., Slama A., Ioos C., Desguerre I., Lebre A.-S., de Lonlay P., Christa L., Pedespan J.-M., Henrion-Caude A., Damaj L., Odent S., Clot F., Corne C., de Pontual L., Bahi-Buisson N., Martinez G., Gaillard R., Krebs M.-O.	Diagnostic approach to neurotransmitter monoamine disorders: experience from clinical, biochemical, and genetic profiles
2017	Poniah P., Mohd Zain S., Abdul Razack A.H., Kuppusamy S., Karuppayah S., Sian Eng H., Mohamed Z.	Genome-wide copy number analysis reveals candidate gene loci that confer susceptibility to high-grade prostate cancer
2017	Christine C., Bankiewicz K., Van Laar A., Richardson M., Ravina B., Kells A., Boot B., Martin A., Thompson M., Larson P.	Intraluminal AADC gene therapy for advanced Parkinson's disease: Interim Results of a Phase 1b Trial
2017	Hwu W.-L., Lee Y.-M., Lee N.-C.	Gene therapy with modified U1 small nuclear RNA
2017	Sherazi N.A., Khan A.H., Jafri L., Jamil A., Khan N.A., Afroze B.	Selective screening for organic acidurias and amino acidopathies in Pakistani children
2017	Larson P.S., Bankiewicz K., Bringas J., Martin A., Richardson R., Van Laar A., Ravina B., Kells A., Thompson M., Christine C.	Real-time MRI-guided delivery of AAV2-AADC gene therapy for Parkinson's disease: Infusion strategies and their impact on coverage of the putamen
2017	Fluegge K.	The new frontier in health services research: A behavioural paradigm guided by genetics
2017	Richarson M., Chadwick C.W., Bankiewicz K.S., Van Laar A., Ravina B., Kells A., Boot B., Larson P.S.	Real-time MRI-guided intraputaminal AADC gene therapy for advanced Parkinson's disease
2017	Ravina B., Christine C., Bankiewicz K., Van Laar A., Richardson M., Kells A., Boot B., Martin A., Thompson M., Larson P.	Intraputaminal AADC gene therapy for advanced Parkinson's disease: Interim results of a phase 1b Trial
2017	Troncoso M., Santander P., Vergara D., Tello J., Naranjo V., Rojas C., Wicki A., Alid P., Gonzalez M.	Monoamine neurotransmitter disorders in a Chilean cohort of infants and children
2016	Gupta M., Neavin D., Liu D., Biernacka J., Hall-Flavin D., Bobo W.V., Frye M.A., Skime M., Jenkins G.D., Batzler A., Kalari K., Matson W., Bhasin	TSPAN5, ERICH3 and selective serotonin reuptake inhibitors in major depressive disorder: Pharmacometabolomics-informed pharmacogenomics

Publication Year	Author	Title
	S.S., Zhu H., Mushiroda T., Nakamura Y., Kubo M., Wang L., Kaddurah-Daouk R., Weinshilboum R.M.	
2016	Mastrangelo M., Giannini M.T., Carducci C.L., Carducci C.A., Leuzzi V.	Safety and efficacy of Rotigotine in 7 patients with monoaminergic neurotransmitter deficiency
2016	Chien Y.-H., Chen P.-W., Lee N.-C., Hsieh W.-S., Chiu P.-C., Hwu W.-L., Tsai F.-J., Lin S.-P., Chu S.-Y., Jong Y.-J., Chao M.-C.	3-O-methyldopa levels in newborns: Result of newborn screening for aromatic L-amino-acid decarboxylase deficiency
2016	Liu Y.-L., Lu M.-Y., Chang H.-H., Lu C.-C., Lin D.-T., Jou S.-T., Yang Y.-L., Lee Y.-L., Huang S.-F., Jeng Y.-M., Lee H., Miser J.S., Lin K.-H., Liao Y.-F., Hsu W.-M., Tzen K.-Y.	Diagnostic FDG and FDOPA positron emission tomography scans distinguish the genomic type and treatment outcome of neuroblastoma
2016	Kraemmer J., Smith K., Weintraub D., Guillemot V., Nalls M.A., Cormier-Dequaire F., Moszer I., Brice A., Singleton A.B., Corvol J.-C.	Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease
2016	Bankiewicz K., Heiss J., Martin A., Bringas J., Zaghloul K., Lason P.	MRI-based platform for AAV2-GDNF and AAV-2AADC gene delivery in Parkinson's disease
2016	Ando Y., Ono S., Nakajima T., Watanabe K., Saga Y., Mizukami H., Watanabe E., Sato T., Ozawa K., Muramatsu S.-I.	The 2nd clinical study of AADC gene therapy for Parkinson disease
2016	Donti T.R., Cappuccio G., Miller M., Atwal P., Kennedy A., Cardon A., Bacino C., Emrick L., Hertecant J., Baumer F., Porter B., Bainbridge M., Bonnen P., Graham B., Sutton R., Sun Q., Elsea S.	Metabolomic profiling for the diagnosis of neurometabolic disorders
2015	Brewka A., Owen T., Lin J.-P., Ajzensztejn M.	Paraphilic compulsion secondary to dopamine replacement therapy and successful treatment with GNRH analogues
2015	Papadopoulos E.I., Petraki C., Gregorakis A., Chra E., Fragoulis E.G., Scorilas A.	L-DOPA decarboxylase mRNA levels provide high diagnostic accuracy and discrimination between clear cell and non-clear cell subtypes in renal cell carcinoma
2015	Seo Y., Hawkins R., Christine C., Larson P., Bankiewicz K.	In vivo quantitative PET/MR imaging of gene expression in Parkinson's Disease
2015	Moreau C., Meguig S., Corvol J.-C., Labreuche J., Vasseur F., Duhamel A., Delval A., Bardyn T., Devedjian J.-C., Rouaix N., Petyt G., Brefel-Courbon C., Ory-Magne F., Guehl D., Eusebio A., Fraix V., Saulnier P.-J., Lagha-Boukbiza O., Durif F., Faighel M., Giordana C., Drapier S., Maltête D., Tranchant C., Houeto J.-L., Debû B., Azulay J.-P., Tison F., Destée A., Vidailhet M., Rascol O., Dujardin K., Defebvre L., Bordet R., Sablonnière B., Devos D.	Polymorphism of the dopamine transporter type 1 gene modifies the treatment response in Parkinson's disease

Publication Year	Author	Title
2015	Manjurano A., Sepulveda N., Nadjm B., Mtove G., Wangai H., Maxwell C., Olomi R., Reyburn H., Drakeley C.J., Riley E.M., Clark T.G.	USP38, FREM3, SDC1, DDC, and LOC727982 Gene Polymorphisms and Differential Susceptibility to Severe Malaria in Tanzania
2014	O'Loughlin J., Sylvestre M.-P., Labbe A., Low N.C., Roy-Gagnon M.-H., Dugas E.N., Karp I., Engert J.C.	Genetic variants and early cigarette smoking and nicotine dependence phenotypes in adolescents
2014	Li Z., Chang S.-H., Zhang L.-Y., Gao L., Wang J.	Molecular genetic studies of ADHD and its candidate genes: A review
2014	Chen H.-F., Chang S.-P., Wu S.-H., Lin W.-H., Lee Y.-C., Ni Y.-H., Chen C.-A., Ma G.-C., Ginsberg N.A., You E.-M., Tsai F.-P., Chen M.	Validating a rapid, real-time, PCR-based direct mutation detection assay for preimplantation genetic diagnosis
2014	Aktuglu Zeybek C., Kiykim E., Zubarioglu T., Cansever S., Thony B., Aydin A.	A rare cause of severe hypotonia in childhood: Aromatic L-amino acid decarboxylase deficiency
2014	Muramatsu S.-I., Fujimoto K.-I., Kato S., Asari S., Mizukami H., Ikeguchi K., Kawakami T., Urabe M., Kume A., Sato T., Watanabe E., Ozawa K., Nakano I.	AADC gene therapy for Parkinson's disease: Four years of follow-up
2014		17th Annual Meeting 2011 Japan Society of Gene Therapy
2014	Muramatsu S.-I.	In vivo imaging in cell and gene therapy for Parkinson's disease
2014	Muramatsu S.-I.	A phase i study of aromatic L-amino acid decarboxylase gene therapy for parkinson7s disease
2014	Devos D., Lejeune S., Cormier-Dequaire F., Tahiri K., Charbonnier-Beaupel F., Rouaix N., Duhamel A., Sablonnière B., Bonnet A.-M., Bonnet C., Zahr N., Costentin J., Vidailhet M., Corvol J.-C.	Dopa-decarboxylase gene polymorphisms affect the motor response to l-dopa in Parkinson's disease
2013	Toma C., Hervás A., Balmaña N., Salgado M., Maristany M., Vilella E., Aguilera F., Orejuela C., Cuscó I., Gallastegui F., Pérez-Jurado L.A., Caballero-Andaluz R., Diego-Otero Y.D., Guzmán-Alvarez G., Ramos-Quiroga J.A., Ribasés M., Bayés M., Cormand B.	Neurotransmitter systems and neurotrophic factors in autism: Association study of 37 genes suggests involvement of DDC
2013	De Bruyn G., Régal L., Wouters L., Jansen K., Buyse G., Lagae L.	AADC deficiency with oculogyric crises as the most specific presenting symptom
2013	Roh J.-L., Wang X.V., Manola J., Sidransky D., Forastiere A.A., Koch W.M.	Clinical correlates of promoter hypermethylation of four target genes in head and neck cancer: A cooperative group correlative study

Publication Year	Author	Title
2013	Minashkin M.M., Salnikova L.E., Lomonosov K.M., Korobko I.V., Tatarenko A.O.	Possible contribution of GSTP1 and other xenobiotic metabolizing genes to vitiligo susceptibility
2013	Pan Y., Luo X., Liu X., Wu L.-Y., Zhang Q., Wang L., Wang W., Zuo L., Wang K.-S.	Genome-wide association studies of maximum number of drinks
2012	Geomela P.-A., Kontos C.K., Yiotakis I., Fragoulis E.G., Scorilas A.	L-DOPA decarboxylase mRNA expression is associated with tumour stage and size in head and neck squamous cell carcinoma: a retrospective cohort study
2012	Shintaku H.	Nationwide epidemiological study of pediatric neurotransmitter disease in Japan
2012	Hwu W.-L., Lee N.-C., Hsieh Y.-D., Lin S.-W., Chien Y.-H.	A murine model of aromatic L-amino Acid Decarboxylase (AADC) deficiency
2012	Lee H.C.H., Lai C.-K., Yau K.C.E., Siu T.-S., Mak C.M., Yuen Y.-P., Chan K.-Y., Tam S., Lam C.-W., Chan A.Y.W.	Non-invasive urinary screening for aromatic L-amino acid decarboxylase deficiency in high-prevalence areas: A pilot study
2012	Grigoratos D.N., Lumsden D.E., Mahendrakar R., Mundy H.R., Heales S., Lim M.	CSF neurotransmitter analysis in routine clinical neurology practice: A review of utility in clinical management
2010	Muramatsu S.-I., Asari S., Fujimoto K.-I., Ozawa K., Nakano I.	Gene therapy for Parkinson's disease: Strategies for the local production of dopamine
2010	Muramatsu S.-I., Fujimoto K.-I., Kato S., Mizukami H., Asari S., Ikeguchi K., Kawakami T., Urabe M., Kume A., Sato T., Watanabe E., Ozawa K., Nakano I.	A phase i study of aromatic L-amino acid decarboxylase gene therapy for Parkinson's disease
2010	Kontos C.K., Papadopoulos I.N., Fragoulis E.G., Scorilas A.	Quantitative expression analysis and prognostic significance of L-DOPA decarboxylase in colorectal adenocarcinoma
2010	Costas J., Gratacòs M., Escaramís G., Martín-Santos R., de Diego Y., Baca-García E., Canellas F., Estivill X., Guillamat R., Guitart M., Gutiérrez-Zotes A., García-Esteve L., Mayoral F., Dolores Moltó M., Phillips C., Roca M., Carracedo T., Vilella E., Sanjuán J.	Association study of 44 candidate genes with depressive and anxiety symptoms in post-partum women
2009	Morimoto B.	Drug development for neurodegenerative diseases - A marcus evans conference
2007	Mochizuki H.	Gene therapy for Parkinson's disease

Publication Year	Author	Title
2006	Kwon M.-O., Herrling P.	List of drugs in development for neurodegenerative diseases
2006	Yu Y., Panhuysen C., Kranzler H.R., Hesselbrock V., Rounsaville B., Weiss R., Brady K., Farrer L.A., Gelernter J.	Intronic variants in the dopa decarboxylase (DDC) gene are associated with smoking behaviour in European-Americans and African-Americans
2006	Sorbera L.A.	CERE-120: Antiparkinsonian drug gene therapy
2005	Kwon M.-O., Herrling P.	List of drugs in development for neurodegenerative diseases: Update September 2005
2005	Mealy N.E., Bayés M.	Treatment of neurological disorders
2002	Jahnes E., Müller D.J., Schulze T.G., Windemuth C., Cichon S., Ohlraun S., Fangerau H., Held T., Maier W., Propping P., Nöthen M.M., Rietschel M.	Association study between two variants in the DOPA decarboxylase gene in bipolar and unipolar affective disorder
1998	Fan D.-S., Ogawa M., Fujimoto K.-I., Ikeguchi K., Ogasawara Y., Urabe M., Nishizawa M., Nakano I., Yoshida M., Nagatsu I., Ichinose H., Nagatsu T., Kurtzman G.J., Ozawa K.	Behavioural recovery in 6-hydroxydopamine-lesioned rats by cotransduction of striatum with tyrosine hydroxylase and aromatic L-amino acid decarboxylase genes using two separate adeno-associated virus vectors
2020	Senek, M; Nyholm, D; Nielsen, EI	Population pharmacokinetics of levodopa gel infusion in Parkinson's disease: effects of entacapone infusion and genetic polymorphism
2020	Nutt, JG; Curtze, C; Hiller, A; Anderson, S; Larson, PS; Van Laar, AD; Richardson, RM; Thompson, ME; Sedkov, A; Leinonen, M; Ravina, B; Bankiewicz, KS; Christine, CW	Aromatic L-amino Acid Decarboxylase Gene Therapy Enhances Levodopa Response in Parkinson's Disease
2018	NCT03562494,	VY-AADC02 for Parkinson's Disease With Motor Fluctuations
2012	Modak, A; Durso, R; Josephs, E; Rosen, D	A rapid non invasive L-DOPA-Â¹Â³C breath test for optimally suppressing extracerebral AADC enzyme activity - toward individualizing carbidopa therapy in Parkinson’s disease
2003	Kaufmann, H; Saadia, D; Voustianiouk, A; Goldstein, DS; Holmes, C; Yahr, MD; Nardin, R; Freeman, R	Norepinephrine precursor therapy in neurogenic orthostatic hypotension
2012	NCT01568073,	Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients With "Wearing-off" Phenomenon

Publication Year	Author	Title
2010	NCT01227655,	Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients
2017	NCT03103399,	Efficacy and Tolerability of Nebicapone in Parkinson's Disease Patients With "Wearing off" Phenomenon
2014	Devos, D; Lejeune, S; Cormier-Dequaire, F; Tahiri, K; Charbonnier-Beaupel, F; Rouaix, N; Duhamel, A; SablonniÃ¨re, B; Bonnet, AM; Bonnet, C; Zahr, N; Costentin, J; Vidailhet, M; Corvol, JC	Dopa-decarboxylase gene polymorphisms affect the motor response to L-dopa in Parkinson's disease
2012	Modak, A; Durso, R; Josephs, E; Rosen, D	A rapid non-invasive L-DOPA-13C breath test for optimally suppressing extracerebral AADC enzyme activity - Toward individualizing carbidopa therapy in Parkinson's disease

D1.1.7 Complete reference lists for included studies and excluded studies

Table 96: Summary of all clinical publications (n=38)

Study	Reference
Chien *et al.* 2021[138]	Yin-Hsiu Chien, Paul Wuh-Liang Hwu, Ni-Chung Lee *et al.* 2021 *Improved motor function in children with aromatic L-amino acid decarboxylase (AADC) deficiency treated with eladocagene exuparvovec (PTC-AADC): Interim findings from a phase 2 trial*
Hwu *et al.* 2021 (NCT01395641, NCT02926066)[40]	Paul Wuh-liang Hwu, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2021 *Eladocagene exuparvovec gene therapy improves motor development in patients with aromatic L-amino acid decarboxylase deficiency*
Hwu *et al.* 2021 (NCT01395641, NCT02926066)[139]	Paul Wuh-liang Hwu, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2021 *Eladocagene exuparvovec improves body weight and reduces respiratory infections in patients with aromatic I-amino acid decarboxylase deficiency*
Hwu *et al.* 2021 (NCT01395641, NCT02926066)[140]	Paul Wuh-liang Hwu, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2021 *Gene Therapy with Eladocagene Exuparvovec Improves Cognition and Language in Patients with Aromatic L-amino Acid Decarboxylase Deficiency*
Hwu *et al.* 2021[141]	Paul Wuh-Liang Hwu, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2021 *Improved Motor Function in Children With Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Treated With Eladocagene Exuparvovec (PTC-AADC): Compassionate Use Study (2387),* 10.1016/j.jval.2021.04.1035

Study	Reference
Hwu *et al.* 2021 (NCT01395641, NCT02926066)[142]	Paul Wuh-liang Hwu, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2021 *Reductions in oculogyric crisis duration and frequency in children with aromatic L-amino acid decarboxylase deficiency treated with eladocagene exuparvovec gene therapy: results from 3 clinical trials*
Hwu *et al.* 2021[143]	PWL Hwu, PE Pachelli, YH Chien *et al.* 2021 *Safety And Improved Efficacy Outcomes In Children With Aadc Deficiency Treated With Eladocagene Exuparvovec Gene Therapy: Results From Three Clinical Trials* Cytotherapy, 10.1016/j.jcyt.2021.02.095
Pearson *et al.* 2021 (NCT02852213)[144]	Toni S. Pearson, Nalin Gupta, Waldy San Sebastian *et al.* 2021 *Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons* Nature Communications, 10.1038/s41467-021-24524-8
Saberian *et al.* 2021[112]	Saberian S, Rowan P, Patel P *et al.* 2021 *Disease Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Healthcare Resource Use (HCRU) Overall and by Disease Severity,* Value in Health
Williams *et al.* 2021[51]	Kate Williams, Hanna Skrobanski, Christian Werner *et al.* 2021 *Symptoms and impact of aromatic L-amino acid decarboxylase (AADC) deficiency: a qualitative study and the development of a patient-centred conceptual mode,* Current Medical Research and Opinion, 10.1080/03007995.2021.1932449
Chien *et al.* 2020[145]	Yin-Hsiu Chien, Paul Wuh-Liang Hwu, Ni-Chung Lee *et al.* 2020 *Improved Motor Function in Children with AADC Deficiency Treated with Eladocagene Exuparvovec (PTC-AADC): Interim Findings from a Phase 2 Trial,* Molecular Therapy
Gupta *et al.*[74]	Nalin Gupta, Toni Pearson, Jill Imamura-Ching *et al.* 2020 *Gene Therapy for the Treatment of Primary L-Aromatic Amino Acid Decarboxylase Deficiency in Children* Journal of Neurosurgery, 10.3171/2020.4
Hwu *et al.* 2020[146]	P Wuh-Liang Hwu, Y Chien1, N Lee *et al.* 2020 *Improved motor function in children with AADC deficiency treated with eladocagene exuparvovec (PTC-AADC): compassionate use study,* Developmental Medicine & Child Neurology, 10.1111/dmcn.14662
Hwu *et al.* 2020[147]	Paul Wuh-Liang Hwu, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2020 *Improved Motor Function in Children with AADC Defi ciency Treated with Eladocagene Exuparvovec (PTC-AADC): Interim Findings from a Phase 1/2 Study,* Molecular Therapy, 10.1016/j.ymthe.2020.04.019
Pearson *et al.* 2020 (NCT02852213)[7]	Toni S. Pearson, Laura Gilbert, Thomas Opladen *et al.* 2020 *AADC deficiency from infancy to adulthood: Symptoms and developmental outcome in an international cohort of 63 patients,* Journal of Inherited Metabolic Disease, 10.1002/jimd.12247
Wen *et al.* 2020[44]	Yongxin Wen, Jiaping Wang, Qingping Zhang *et al.* 2020

Study	Reference
	The genetic and clinical characteristics of aromatic L-amino acid decarboxylase deficiency in mainland China, Journal of Human Genetics, 10.1038/s10038-020-0770-6
Bankiewicz *et al.* 2019[75]	K. Bankiewicz, T. Pearson, A. Grijalvo-Perez *et al.* 2019 *Restoring AADC enzyme synthesis in AADC deficiency: MRI-Guided Delivery of AAV2-hAADC Gene Therapy to the Midbrain*
Chien *et al.* 2019[67]	Y.H. Chien, N.C. Lee, S.H. Tseng *et al.* 2019 *AGIL-AADC gene therapy results in sustained improvements in motor and developmental milestones through 5 years in children with AADC deficiency,*Journal of the Neurological Sciences, 10.1016/j.jns.2019.10.261
Hwu *et al.* 2019[148]	Hwu P W-L, Chien Y-H, Lee N-C *et al.* 2019 *Safety and Improved Efficacy Outcomes in Children with AADC Deficiency Treated with AGIL-AADC Gene Therapy: Results from Three Clinical Trials,* Annals of Neurology
Mastrangelo *et al.* 2019[81]	Mastrangelo M, Baglioni V, Cesario S *et al.* 2019 *Neurocognitive and motor outcome in five patients with Aromatic L-amino Acid Decarboxylase deficiency,* Journal Inherited Metabolic Disease, 10.1002/jimd.12153
Pearson *et al.* 2019[149]	Pearson T, Gupta N, Grijalvo-Perez A *et al.* 2019 *Gene Therapy for AADC deficiency: MRI-Guided Delivery of AAV2-hAADC to the Midbrain,* Annals of Neurology
Werner *et al.* 2019[150]	Christian Werner, Yin-Hsiu Chien, Ni-Chung Lee *et al.* 2019 *AGIL-AADC Gene Therapy Results in Sustained Improvements in Motor and Developmental Milestones over 5 Years in Children with AADC Deficiency,* Neuropediatrics, 10.1016/j.ymgme.2020.07.001
Bankiewicz *et al.* 2018[77]	Krystof Bankiewicz, Toni Pearson, Amy Viehoever *et al.* 2018 *Dose escalation gene therapy trial in children with AADC deficiency,* Molecular Therapy
Chien *et al.* 2018[151]	Chien Y H, Lee N C, Tseng S H *et al.* 2018 *AGIL-AADC gene therapy in children with AADC deficiency increases dopamine production and sustains motor milestones,* Journal of Inherited Metabolic Disease, 10.1007/s10545-018-0233-9
Chien *et al.* 2018[152]	Chien Y, Lee N, Tseng S *et al.* 2018 *Gene Therapy with AGIL-AADC in Children with AADC Deficiency Leads to De Novo Dopamine Production and Sustained Improvement in Motor Milestones Over 5 Years,* Annals of Neurology, 10.1002/ana.25305
Lee *et al.* 2018[153]	Ni-Chung Lee, Yin-Hsiu Chien, Sheng-Hong Tseng *et al.* 2018 *Gene Therapy for AADC Deficiency Results in De Novo Dopamine Production and Supports Durable Improvement in Major Motor Milestones,* Molecular Therapy

Study	Reference
Chien *et al.* 2017[34] (NCT01395641, NCT02926066)	Yin-Hsiu Chien, Ni-Chung Lee, Sheng-Hong Tseng *et al.* 2017 *Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial,* The Lancet Child & Adolescent Health, 10.1016/S2352-4642(17)30125-6
Hwu *et al.* 2017[154]	Wuh-Liang Hwu, Ni-Chung Lee, Shin-ichi Muramatsu *et al.* 2017 *Gene Therapy for Aromatic L-amino Acid Decarboxylase Deficiency: 5 Years After AAV2- hAADC Transduction,* Molecular Therapy
Lee *et al.* 2017[155]	Ni-Chung Lee, Yin-Hsiu Chien, Shin-ichi *et al.* 2017 *A Phase I/II Trial of Gene Therapy for an Inherited Disorder of Monoamine Neurotransmitter Deficiency,* Molecular Therapy
Hwu *et al.* 2015[156]	Wuh-Liang Hwu, Shin-Ichi Muramatsu, Ni-Chung Lee *et al.* 2015 *An Update on Gene Therapy for the Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency,* Molecular Therapy
Chan *et al.* 2012[79]	K-Y Chan, E Yau, G Ng *et al.* 2012 *Paediatric neurotransmitter disease: experiences of a regional hospital,* Developmental Medicine & Child Neurology, 10.1111/j.1469-8749.2012.04283.x
Tai *et al.,* 2022[157]	Tai *et al.,* 2022 *Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency*
Bergkvist *et al.,* 2021[8]	Bergkvist *et al.,* 2021
Boenkhe *et al.,* 2021[158]	Boenkhe *et al.,* 2021 *Gene Therapy for Rare Diseases: Differences to Chronic Therapy and the Example of AADC Deficiency*
Boenkhe *et al.,* 2021[159]	Boenkhe *et al.,* 2021 *POSC206 How Gene Therapy for Rare Diseases Differs from Chronic Therapy: The Case of AADC-d*
Havali *et al.,* 2021[83]	Havali *et al.,* 2021 *Approaches for diagnosis and treatment in neurotransmitter disorders of childhood.*
Ling *et al.,* 2021[160]	Ling *et al.,* 2021 *Urine organic acid as the first clue towards aromatic L-amino acid decarboxylase (AADC) deficiency in a high prevalence area.*
Saberian *et al.,* 2021[112]	Saberian *et al.,* 2021 *POSA192 Disease Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Signs and Symptoms*

Abbreviations: 5-HIAA – 5-Hydroxyindoleacetic acid; AADC – Aromatic L-amino acid decarboxylase deficiency; AAV2 – Adeno-associated virus serotype 2; AE – Adverse event; AIMS – Abnormal Involuntary Movement Scale; Bayley-III – Bayley Scales of Infant and Toddler Development, Third Edition; CED – Convection enhanced delivery; CSF – Cerebral spinal fluid; CU – Compassionate-use; F-DOPA – Fluorodopa; HCRU – Healthcare resource utilization; HVA – Homovanillic acid; iNTD – The International Working Group of Neurotransmitter-Related Disorders; MAO-I – Monoamine oxidase inhibitor; OGC – Oculogyric crisis; PDMS-2 – Peabody Developmental Motor Scale, Second Edition; PET – Positron emission tomography; PND – Paediatric neurotransmitter disease; SNc – Substantia nigra; TEAE – Treatment-emergent adverse event; TH – tyrosine hydroxylase; UCSF – University of California, San Francisco; vg – vector genomes; VTA – Ventral tegmental area

Table 97: List of relevant published clinical effectiveness evidence for eladocagene exuparvovec treatment (n=23)

Reference	Primary source	Population	Intervention	Reported outcomes (bold in model)
Hwu *et al*. 2021[141]	AADC-CU/1601: Compassionate use study	AADC-CU/1601: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg	Primary efficacy endpoint: proportion achieving key milestones at 5 years using PDMS-2, compared with historical control (n=82). Secondary endpoints: changes from baseline in PDMS-2, AIMS, and CDIIT scores and body weight, and neurological examination findings. Pharmacodynamic endpoint was putaminal F-DOPA uptake on PET. Safety endpoints included TEAEs and viral shedding. Mean follow-up duration was 62.5 months
Hwu *et al*. 2021[143]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old.	Body weight, oculogyric crisis episodes, and AEs were recorded.
Hwu *et al*. 2020[146]	AADC-CU/1601: Compassionate use study	AADC-CU/1601: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg	Primary efficacy endpoint: proportion achieving key milestones at 5 years using PDMS-2, compared with historical control (n=82). Secondary endpoints: changes from baseline in PDMS-2, AIMS, and CDIIT scores and body weight, and neurological examination findings. Pharmacodynamic endpoint was putaminal F-DOPA uptake on PET. Safety endpoints included TEAEs and viral shedding. Mean follow-up duration was 62.5 months
Hwu *et al*. 2020[145]	AADC-010 (phase I/II): NCT01395641	AADC-010: Children aged 2+ years with AADC deficiency	AADC-010: eladocagene exuparvovec 1.8×10^11 vg	Primary efficacy endpoint: proportion achieving key milestones at 5 years using PDMS-2, compared with historical control (n=82). Secondary endpoints: changes from baseline in PDMS-2, AIMS, and CDIIT scores and body weight, and neurological examination findings. Pharmacodynamic endpoint was putaminal F-

				DOPA uptake on PET. Safety endpoints included TEAEs and viral shedding. Mean follow-up duration was 62.5 months
Chien *et al*. 2020[145]	AADC-011 (phase II): NCT02926066	AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old.	Primary efficacy endpoint: proportion achieving key milestones at 5 years using PDMS-2, compared with historical control (n=82). Secondary endpoints: changes from baseline in PDMS-2, AIMS, and CDIIT scores and body weight, and neurological examination findings. Pharmacodynamic endpoint was putaminal F-DOPA uptake on PET. Safety endpoints included TEAEs and viral shedding. Mean follow-up duration was 62.5 months
Chien *et al*. 2019[67]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg	The primary endpoint was improvement on the PDMS-2. The AIMS and Bayley-III also assessed developmental milestones. De novo dopamine production was evaluated with 6-fluorodopa PET imaging. Adverse events were recorded. Findings were compared with those from a natural history cohort of severe AADC patients (N=82)
Hwu *et al*. 2019[148]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old.	Body weight, oculogyric crisis episodes, and AEs were recorded.
Chien *et al*.2021[138]	AADC-011 (phase II): NCT02926066	AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Primary efficacy end point: proportion achieving key milestones using PDMS-2. Secondary end points included changes in PDMS-2, AIMS, Bayley-III, and body weight. Pharmacodynamic end points included putaminal F-DOPA uptake on PET.

Werner *et al*. 2019[150]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg	Primary endpoint: Achievement of motor developmental milestones on the PDMS-2 total and subscale scores, total and subscale scores on the AIMS, Bayley-III and assessed developmental milestones. De novo dopamine production was evaluated with fluorodopa PET imaging. AEs were recorded. Findings were compared with those from a natural history cohort of severe AADC patients (n=82).
Chien *et al*. 2018[152]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg	De novo dopamine production was evaluated using F-DOPA PET imaging. Clinical assessments included the achievement of motor milestones and adverse events (AEs). Data from AGIL-AADC patients were compared with a natural history cohort of severe AADC patients using Fisher exact test (a=0.05).
Hwu *et al.* 2021[40]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Proportion achieving key milestones using PDMS-2, AIMS, and CDIIT scores, and neurological examination findings.
Chien *et al.* 2018[151]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg	De novo dopamine production was evaluated using F-DOPA PET imaging. Clinical assessments included the achievement of motor milestones and adverse events (AEs). Data from AGIL-AADC patients were compared with a natural history cohort of severe AADC patients using Fisher exact test (a=0.05).

Lee *et al.* 2018[161]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Motor milestones (full head control, sitting unassisted, standing with support standing unassisted)
Chien *et al.* 2017[34]	AADC-010 (phase I/II): NCT01395641	AADC-010: Children aged 2+ years with AADC deficiency	AADC-010: eladocagene exuparvovec 1.8×10^11 vg	Primary efficacy outcomes were an increase in the PDMS-2 score of greater than 10 points and an increase in HVA or 5-HIAA concentrations in the cerebrospinal fluid 12 months after gene therapy.
Hwu *et al.* 2021[142]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Proportion of patients reporting OGC episodes, duration of OGC episodes, frequency of OGC episodes, percentage of time spent in OGC episodes,
Hwu *et al.* 2021[139]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Percentage of patients experiencing respiratory infections and pneumonia, annual rate of respiratory infections, TEAEs number and type, body weight
Lee *et al.* 2017[155]	AADC-010 (phase I/II): NCT01395641	AADC-010: Children aged 2+ years with AADC deficiency	AADC-010: eladocagene exuparvovec 1.8×10^11 vg	Motor scales, cerebral spinal fluid neurotransmitter concentrations, and tracer uptake in F-DOPA PET. Anti-AAV2 antibody titres. No signs of cerebral or systemic immune reaction during the follow-up period
Hwu *et al.* 2017[154]	AADC-CU/1601: Compassionate use study	AADC-CU/1601: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg	Motor development and cognitive function showed improvement. At 5 years after gene transduction, F-DOPA PET still exhibited signals of AADC activity over the putamina. Patients' anti-AAV2 antibody titres rose

				after gene transduction, peaked a few months later, and then decreased. There were no signs of cerebral or systemic immune reaction during the follow-up period
Hwu *et al.* 2015[156]	AADC-CU/1601: Compassionate use study	AADC-CU/1601: Children aged 2+ years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg	Motor milestones (walking, standing with support, sitting without assistance, head control), OGC severity, flouro-dopa PET signal intensity. AEs also recorded.
Hwu *et al.* 2021[140]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Cognition and language changes were assessed using the CDIIT and Bayley-III scores.
Tai *et al.*, 2022[10]	AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	• Motor functioning/ milestones • Speech and language development • Neurotransmitter metabolite HVA and 5-HIAA levels in CSF • Putaminal signal of 6-[F]fluorodopa-PET • Safety
Boenkhe *et al.*, 2021[158]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Motor functioning/ milestones
Boenkhe *et al.*, 2021 [78]	AADC-CU/1601: Compassionate use study AADC-010 (phase I/II): NCT01395641 AADC-011 (phase II): NCT02926066	AADC-CU/1601: Children aged 2+ years with AADC deficiency AADC-010: Children aged 2+ years with AADC deficiency AADC-011: Children aged 2 - 6 years with AADC deficiency	AADC-CU/1601: eladocagene exuparvovec 1.8×10^11 vg AADC-010: eladocagene exuparvovec 1.8×10^11 vg AADC-011: eladocagene exuparvovec 1.8×10^11 vg to patients 3+ years old. 2.4 × 10^11 vg to patients <3 years old	Motor functioning/ milestones

Abbreviations: AADC– Aromatic L-amino acid decarboxylase; AADC deficiency – Aromatic L-amino acid decarboxylase deficiency; AAV2 - Anti-adeno-associated virus serotype 2; AE – Adverse event; AIMS – Alberta Infant Motor Scale; Bayley-III – Bayley Scales of Infant Development 3rd edition: CDIIT – Comprehensive Developmental Inventory for Infants and Toddlers; F-DOPA - L-6-fluoro-3, 4-dihydroxyphenylalnine; HIAA – hydroxyindoleacetic acid; HVA – homovanillic acid; OGC – Oculogyric crises; PDMS-2 – Peabody Developmental Motor Scale 2nd edition; PET – Positron emission tomography; TEAEs – Treatment-emergent adverse events

D1.1.8 Summary of trials used for indirect or mixed treatment comparisons

A summary of the trials considered in the ITC feasibility analysis considered in this NICE appraisal are given in Table 98.

Table 98: Studies utilised in the ITC feasibility analyses

Therapy	Trial name
Eladocagene exuparvovec	AADC-CU/1601[16]
	AADC-010[18]
	AADC-011[17]
Natural history/BSC	Natural history database[46, 8]

Abbreviations: BSC – Best supportive care; ITC – indirect treatment comparison

Methods and outcomes of studies included in indirect or mixed treatment comparisons

Eladocagene exuparvovec trials

The three intervention clinical trials (AADC-010[18], AADC-011[17] and AADC-1601[16]), are described in detail in Section B.2.3.

NHDB and SLR methodology

Background and objectives

To date, no long-term observational studies have been performed evaluating the natural history of AADC deficiency. Wassenberg *et al.* (2017)[2] published an SLR of all available reported cases of AADC deficiency through to 2015, providing insights into the natural history of the disease in aggregate form. Thus, an NHDB literature review was conducted (and described in Bergkvist *et al*., 2021[8]) based on the SLR conducted by Wassenberg *et al.* (2017)[2] and was intended to collect up-to-date data on AADC deficiency cases reported in the literature. Capturing these data by patient allows for greater evaluation of the natural history of the disease than using the Wassenberg *et al.* (2017)[2] SLR alone.

The aim of the NHDB SLR was to create a patient-level natural history cohort as a control to evaluate the efficacy of eladocagene exuparvovec in treating AADC deficiency.

The primary efficacy assessment is attainment of the sequential motor milestones of:

- Full head control
- Sitting unassisted
- Standing with support
- Walking with assistance.

Publicly available databases were searched for all published literature to identify case reports of patients with AADC deficiency up to December 2019.[8] Included papers and relevant review articles were searched for additional sources.[8] No language filter was used.[8]

Eligibility criteria

The following publications/abstracts/presentations were included in the NHDB:[8]

- Case and case series reports of patients with diagnosed AADC deficiency
- Clinical studies of patients with diagnosed AADC deficiency
- Conference abstracts of patients diagnosed with AADC deficiency, if the data were not presented in a subsequent publication
- Literature reviews of publications and analysis of subjects with AADC deficiency

Publications were excluded if they did not describe patient-specific clinical characteristics.

Information sources

The following databases were searched through 20 December 2019:[8]

- BIOSIS Previews
- Embase
- MEDLINE

Grey literature searching included:

- Reference list from the official website of the AADC Research Trust were searched for applicable articles (https://www.aadcresearch.org/cronological-order-with-links)
- Reference list of review publications and included case-reports and case series were searched

Search strategy

The database search strategy is summarised in Table 99.[8]

Table 99: Search strategy

Set	Databases	Searched for
S1	MEDLINE®	((MJMESH.EXACT("Aromatic-L-amino-Acid Decarboxylases")) OR (aromatic L-aminoacid decarboxylase deficiency) OR (AADC)and (human(yes))
S2	Embase®	((MJEMB.EXACT("aromatic levo amino acid decarboxylase")) OR (aromatic L-amino acid decarboxylase deficiency) OR AADC)and (human(yes))
S3	BIOSIS Previews®	((aromatic L-amino acid decarboxylase deficiency) OR AADC)and (human(yes))
S4	BIOSIS Previews®, Embase®, MEDLINE®	S3 OR S2 OR S1

Selection process

Two independent reviewers screened the results from the database searches for eligibility and inclusion of publications into the review. A third independent reviewer adjudicated any discrepancies.[8]

NHDB methodology

Overview

To characterize the natural history of AADC deficiency, an extensive literature search was compiled of all reports of patients with AADC deficiency described in the literature up to 20 December 2019.[162]

All cases of AADC deficiency identified in the literature review were entered into the NHDB. Data from the publications were entered "as-is" (i.e., copied or transcribed or key information extracted) with adjudications performed as part of a separate analysis phase. The final NHDB includes 3 tables, which are connected in a hierarchical manner in a one-to-many relationship. The hierarchy of the tables consists of: publication, subject demographics, and subject detail data. Once the data were entered for all publications, subjects reported in multiple publications were identified and recorded.[162]

Database and design structure

The NHDB was designed in an iterative manner. A subset of the publications was selected to determine and define the structure for the database. The subjects were entered into the database including all detailed information. Once several subjects were entered, adjudication of the subject information was attempted. Upon review, the data was classified, definitions determined, and formats defined and applied to ensure consistency in data entry and for analytical purposes. [162]

The structure determined to support the application in the most beneficial manner was hierarchical. Three levels were identified for the database structure.

1. Publication – based on the Protocol – Include individual subjects with AADC deficiency and prior to GT, if provided
2. Subject demographics – one per publication
3. Subject detail records – one or multiple per subject and publication.

The first level was created to account for the publications reviewed, prioritized based on the definition in the protocol. They were entered and cross-referenced to a literature database in EndNote. All publications reviewed were included and the publications that contained subjects with AADC deficiency were identified and noted. [162]

In the second level, each subject with AADC deficiency from each publication was entered into a demographics table. The table contained descriptive information for the subject, if available, including sex, age of diagnosis, mutation, ethnicity, and when deceased. Each subject in a publication has one record. [162]

The third level of the database structure details the specifics of the subject's medical history and disease progression. Details include the treatments administered, motor development, and symptoms. Each subject has the possibility of multiple entries in the table, depending on the details provided in the publication. [162]

Data entry

The NHDB is based on published materials regarding subjects that have been diagnosed with AADC deficiency. Table 100 describes the steps taken to identify the publications to be evaluated for inclusion in NHDB. [162]

In steps 1–3, three different database searches were executed. A total of 1558 matches were returned. In step 4 the unique publications were identified, and 501 duplications were eliminated. 1057 publications remained to be reviewed.

In step 5, a title and abstract review was performed to determine that the publications containing specific discussions regarding subjects with AADC deficiency. A total of 119 publications were identified for detailed review, of which 55 articles and 43 abstracts (98 publications in total) were considered for inclusion, and ultimately included, in the NHDB.[162]

Table 100: NHDB publication review process

Step	Action	Searched for	Results
1	MEDLINE® search	((MJMESH.EXACT("Aromatic-L-amino-Acid Decarboxylases")) OR (aromatic L-amino acid decarboxylase deficiency) OR AADC) and (human(yes))	392 hits
2	Embase® search	((MJEMB.EXACT("aromatic levo amino acid decarboxylase")) OR (aromatic L-amino acid decarboxylase deficiency) OR AADC) and (human(yes))	813 hits
3	BIOSIS Previews® search	((aromatic L-amino acid decarboxylase deficiency) OR AADC) and (human(yes))	353 hits
4	A combined search of BIOSIS Previews®, Embase® and MEDLINE® to remove duplicates.	NA	1057
5	Publication title and abstract review	NA	119
6	Full-text content review	NA	55 articles attachment

Publication review and data entry

The articles and abstracts that contained subjects with detailed information were read and analysed in detail, and the demographic and detailed data were entered per the publication.[162]

QC process

Quality control occurred on a publication-by-publication basis through a third party. Upon finalisation, all QC comments were included and accounted for.[162]

Process to identify unique subjects

Publications fell into one of the four categories detailed below. As a result, unique subjects were able to be identified.[162]

Direct and independent (assign unique subject id)

- Independent/external with uniquely identified subjects
- Subject explicitly linked to subjects in other publications (e.g. a current publication link)

Deduced (assign unique subject id)

- High: demographics and subject detail available and match; authors of institutions align
- Medium: predominate demographics and subject detail attributes available and match
- Low: some demographics and subject detail attributes available and match. For example: one publication may describe subjects in high-level of detail from a specific site or region of country; whereas a second publication describes subjects from the same site or region but with limited demographics information, meaning it is hard to decide whether this is a unique subject already identified or a new unique subject should be added.
- When the identification of the subject was “Direct and independent” and no deduction is necessary.

Little or no demographics and subject detail available (assigned subject id = 99999)
For example, 7 AADC deficiency subjects identified, of which all 7 had the same characteristics.

No individual subject information available (assigned subject id = 99999)
For example, 7 subjects were identified, some of which had AADC deficiency but it was not defined whom or how many.

Using this methodology, 237 unique subjects were identified at finalisation. Subject demographics that were identified included:

- Sex
- Age of diagnosis
- Mutation 1
- Mutation 2
- Baseline AIMS
- Baseline PDMS-2
- Severity
- Country of treatment
- Ethnicity

- Race
- Country analysed or reported in
- Age of death
- Included in PTC study
- Unique NHDB subject ID#
- Quality of data
- Deduction

Methods of analysis of studies included in the indirect or mixed treatment comparison

Propensity score matching aims to control for self-selection and extend causal inference into non-randomized studies.[163] Propensity scores, which give the conditional probability of assignment to a particular treatment or control given a set of patient baseline covariates, are estimated for each patient. In this analysis, these propensity scores have been calculated using logistic regression.

Propensity scores are then used to match treated patients (in this case those patients in the eladocagene exuparvovec studies) to an untreated patient (in this case those patients in the NHDB receiving BSC). The underlying assumption of propensity score matching is that those patients in the NHDB can be compared to those patients in the eladocagene exuparvovec studies based on the baseline characteristics used to estimate the propensity scores. All analysis has been carried out using the *MatchIt* package in R.

Programming language for the indirect or mixed treatment comparison

The feasibility of the indirect treatment comparison analyses was carried out in R.

Risk of bias of studies included in indirect or mixed treatment comparisons

As it was only feasible to conduct a naïve comparison between eladocagene exuparvovec and the NHDB, there is a risk of bias. An adjusted ITC was not appropriate with the available data due to limited sample size and suboptimal matching.

D1.2 Participant flow in the relevant randomised control trials

Due to the ultra-rare and severe nature of AADC deficiency, all clinical trials considered in this NICE appraisal are open-label, single-arm, non-RCTs. For ethical reasons, trials were not able to include a control arm or placebo, applying a natural history group for comparison to eladocagene exuparvovec patients, as opposed to comparators. Consequently, some parts detailed in the instructions for this section have not been reported, where necessary.

Study ineligible patient numbers and rationale

As seen in Table 101, no patients failed the presurgical screening process, with all screened patients entering the studies.

Table 101: Ineligible patients across the three clinical trials[16,18,17,72,73]

Study	Ineligible patients and rationale
AADC-010	No patients failed presurgical screening. All patients entered the study.
AADC-011	No patients failed presurgical screening. All patients entered the study
AADC-CU/1601	All patients entered the study.

Abbreviations: CSR – Clinical study report
Source: Clinical study report and statistical analysis report for AADC-CU/1601, AADC-010 and AADC-011

As seen in Table 102, across the three studies, 2 patients were lost to follow-up and 1 patient was withdrawn per investigator decision.

Table 102: Patient withdrawal across the studies[16,18,17,72,73]

Study	Number of patients withdrawn or lost to follow-up	Reason for withdrawal/loss to follow-up
AADC-010	1 patient withdrew between month 12 and month 24	Withdrawn per investigator decision and died after 12.2 months of follow-up.
AADC-011	No patients withdrew or were lost to follow-up.	N/A
AADC-CU/1601	2 patients were lost to follow-up between month 24 and month 60	The inability to attend the month 60 visit.

Abbreviations: N/A – Not available
Source: Clinical study report and statistical analysis report for AADC-CU/1601, AADC-010 and AADC-011

Patient treatment allocation across the three clinical studies is detailed in Table 103. Eladocagene exuparvovec was delivered intraputaminally in a single operative session.

Eladocagene exuparvovec was infused into the putamen to treat AADC deficiency. The rationale for the delivery of the gene-replacement therapy into the putamen was as follows:

- Local delivery of eladocagene exuparvovec reduces the chance of expression of AADC enzyme, and possibly misexpression of dopamine or serotonin, in non-targeted areas of the brain and adverse effects
- Delivery of rAAV2-AADC containing the same AAV2 capsid, transgene promoter and ITR's as in eladocagene exuparvovec resulted in AADC protein expression, enzyme activity, and dopamine production in mouse, rats, and non-human primates.
- Injection of the rAAV2-hAADC vector into the bilateral putamen of humans with Parkinson's disease resulted in increased AADC activity and reduction of disease

symptoms. The rAAV2-hAADC vectors used in these studies contained the same wild-type AAV2 capsid and human DDC cDNA as eladocagene exuparvovec.

Table 103: Patient treatment breakdown[16,18,17]

Study	Eladocagene exuparvovec delivery
AADC-010	Dose of 0.45×10^{11} vg and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of 1.8×10^{11} vg and a total volume of 320 µL per subject (n=10).
AADC-011	• $1.8x10^{11}$ vg dose given to patients 3 years and older (n=9). 0.6×10^11 vg and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of 1.8×10^{11} vg and a total volume of 320 µL for each subject • $2.4x10^{11}$ vg dose given to patients less than 3 years old or with sufficient skull thickness (n=3). 0.45×10^11 vector genomes (vg) and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of $2.4x10^{11}$ vg and a total volume of 320 µL for each subject ≥3 years old • Total: n=12
AADC-CU/1601	Dose of 0.45×10^{11} vg and a volume of 80 µl per site to 4 sites (2 per putamen), for a total dose of 1.8×10^{11} vg and a total volume of 320 µl per patient (n=8)

Abbreviations: -
Source: Clinical study report for AADC-CU/1601, AADC-010 and AADC-011

D1.3 Quality assessment for each study

Table 104 displays a quality assessment checklist for publications retrieved in the SLR.

Table 104: Quality assessment checklist for non-RCT publications (n=38)

Publication	Was the cohort recruited in an acceptable way	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	How precise (for example, in terms of confidence interval and p-values) are the results?
Pearson *et al.* 2021[144] (NCT02852213)	Yes Written informed consent was obtained from the legally authorized representative of all study participants. The study was reviewed and approved by the Institutional Review Boards at the University of California San Francisco (Protocol No. 15-17756, approved on 24 June 2016) and The Ohio State University Wexner Medical Centre (Protocol No. 2018H0269, approved on 29 November 2019)	Yes A standard checklist of symptoms of AADC deficiency was evaluated by study investigators, via parent interview, at baseline and at each follow-up evaluation. Each symptom was rated as 'major' (frequent and/or severe), 'minor' (infrequent and/or mild), or absent	Yes Outcome measures assessed safety and biomarker evidence of increased brain AADC activity. Safety of the procedure was evaluated by brain MRI 48 h post-surgery, caregiver report of symptoms at each study visit, neurologist rating of post-surgery involuntary movements (dyskinesia) at each study visit, and caregiver diary of sleep and behaviour symptoms at selected visits. Evidence of NA	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes The duration of post-procedure follow-up is 24–36 months for the 3 subjects in Cohort 1, and 6–18 months for the 4 subjects in Cohort 2	NA Only qualitative outcomes are mentioned

			No information available on authors identified all important confounding factors biological AADC activity was measured by [18F]F-DOPA PET and analysis of CSF neurotransmitter metabolites before and after surgery.				
Hwu *et al.* 2021[141]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes A systematic assessment of adverse events and side effects was performed at each visit with the study neurologist (Screening, Baseline, Weeks 1,2, 4, 5, 6, 7, 8, and Months 3, 6, 12, 18, and 24). Follow-up observations for 7-day periods were recorded in a symptom diary at Week 6 and Months 3, 6, 12, 18 and 24 after surgery.	Yes 4/8 patients exhibited full head control and could sit unassisted (P=0.0002 vs control); 2/8 stood with support (P=0.045 vs control). Mean PDMS-2, AIMS, and CDIIT total scores (all P<0.0001)
Hwu *et al.* 2021[143]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Only qualitative measure for Oculogyric crises outcome	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
Hwu *et al.* 2020[146]	NA	NA	NA	NA	NA	Yes	Yes

	No information available on cohort recruitment	No information available on exposure accurately measured to minimise bias	No information available on the outcome accurately measured to minimise bias	No information available on authors identified all important confounding factors	No information available on authors taken account of the confounding factors in the design and/or analysis	Efficacy of outcomes were given for five years after treatment. The mean follow-up was 62.5 months. Five years post-PTC-ADDC treatment, 4/8 patients exhibited full head control and could sit unassisted (P=0.0002 vs control); 2/8 stood with support (P=0.045 vs control). Mean PDMS-2, AIMS, and CDIIT total scores (all P<0.0001).	4/8 patients exhibited full head control and could sit unassisted (P=0.0002 vs control); 2/8 stood with support (P=0.045 vs control). Mean PDMS-2, AIMS, and CDIIT total scores (all P<0.0001)
Hwu *et al.* 2020[147]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes All completed follow-up through year 1 except 1 patient (withdrawn at 11 months due to influenza B encephalopathy leading to death), and all the others completed follow-up through year 2.	NA No information available in terms of confidence interval and p-values
Chien *et al.* 2020[145]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Mean follow-up was 11.5 months	Yes Increases from baseline in PDMS-2, AIMS, and Bayley-III total scores at 1 year were statistically significant (P<0.0001, P≤0.0016, and

							P≤0.0004 respectively)
Williams *et al.* 2021[51]	Yes. Participants were recruited by a specialist recruitment agency using a variety of sources including social media, patient support groups and clinician referrals.	Yes All interviews were conducted by telephone/ videoconference between September and December 2020. Verbal informed consent was taken at the start of the interview, then the interviews followed the semi-structured interview guide and lasted around an hour.	NA Qualitative measure for outcomes: - Able to stand with minimal support when they were younger, but had regressed and were no longer able to do this. - Several caregivers reported that the individual they cared for had sleep apnoea and around half required ventilation at night in order to support their breathing and maintain their oxygen levels.	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA Only qualitative outcomes are mentioned
Gupta *et al.* 2020[74]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	Yes Qualitative measure for outcomes: Dopamine metabolism (HVA) was increased in all subjects and F-DOPA uptake was enhanced within the SN/VTA and the striatum. By Month 2, OGCs had completely resolved in 5 of the subjects. All subjects achieved gains in head control and voluntary movement at 6-18 months.	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes All subjects achieved gains in head control and voluntary movement at 6-18 months.	NA No information available in terms of confidence interval and p-values

			Two subjects attained the ability to sit independently, weight-bear fully while standing, take steps with support, and reach and grasp with both hands.				
Y.H. Chien *et al.* 2019[67]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	Yes Qualitative measure for outcomes: AGIL-AADC gene-replacement therapy achieved clinically meaningful, sustained improvements in motor, cognitive, and language milestones for up to 5 years, with no new safety signals	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes All patients had at least 2 years of post-treatment data; 8 patients had 5 years post-treatment data.	NA No information available in terms of confidence interval and p-values
Hwu P W-L *et al.* 2019[148]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Only qualitative measure for Oculogyric crises outcome	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Mean body weight increased to 15.2kg at 12 months post-treatment. Frequency of oculogyric crises was improved at 12 months post-treatment.	NA No information available in terms of confidence interval and p-values
Pearson T *et al.* 2019[149]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Qualitative measure for outcomes: - Sleep and mood improved dramatically in all subjects -Motor function	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Motor function improved by 9-30 points at 6-12 months	NA No information available in terms of confidence interval and p-values

			improved by 9-30 points at 6-12 months -CSF homovanillic acid (HVA) increased in all subjects - Increased brain dopamine synthesis - 18FDOPA PET demonstrated increased uptake in the midbrain and striatum				
Chien *et al.* 2021[138]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Only qualitative measure for Oculogyric crises outcome	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes All patients achieved clinically meaningful gains in motor function as measured by PDMS-2, with 50% of patients achieving full head control by month 12 after treatment.	Yes PDMS-2, AIMS, and Bayley-III total scores at 1 year were statistically significant ($P<0.0001$, $P\leq0.0016$, and $P\leq0.0004$, respectively)
Yongxin Wen *et al.* 2020[44]	Yes. Informed consents were obtained from all patients' parents or guardians. Clinical data, including age of onset, clinical manifestations, auxiliary examination, family history, and treatment were collected	NA No information available on exposure accurately measured to minimise bias	No Qualitative measure for outcomes: motor function, mood, autonomic symptoms, sleep disorder, dystonia, hypotonia, oculogyric crises, speech and language development	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values

Mastrangelo M *et al.* 2019[81]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Qualitative measure for outcomes: Remarkable improvement in motor functions and on the asthenic pattern during the time. A relevant improvement was reported in the adaptive behaviors. Reduction of the on–off phenomena was observed in all patients.	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Mean duration of follow-up was 5 years	NA No information available in terms of confidence interval and p-values
Saberian S *et al.* 2021[112]	Yes. A case study questionnaire was developed based on data published in literature and clinician input capturing information about individuals with AADC-deficiency, disease symptoms and HCRU related to the management of the disease.	Yes The questionnaires were completed by experts with experience in treating patients with AADC-deficiency based on information available in the patients' medical records prior to a telephone interview.	Yes Paramedical support was mainly provided by physiotherapists (75% of all patients [60% in patients able to stand/walk with assistance, 50% in patients able to sit, and 100% in patient with no motor function/head control]). All recommended medications were used. Medical device use was higher in patients with no motor function/head control (i.e. 75% needed a manual and/or electric wheelchair). Hospitalisations	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes The median (IQR) duration of follow-up per patient at the time of the survey was 5.00 (2.00 to 7.50) years. At the last follow-up, 19 (95%) patients had a neurologist involved in their medical management.	NA No information available in terms of confidence interval and p-values

			were frequent with a mean (SD) number of hospitalisations since diagnosis of 19.66 (46.03) due to uncontrollable movements.				
Christian Werner *et al.* 2019[150]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	Yes Qualitative measure for outcomes: AGIL-AADC gene-replacement therapy achieved clinically meaningful, sustained improvements in motor, cognitive, and language milestones for up to 5 years, with no new safety signals	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 2 - 5 years	NA No information available in terms of confidence interval and p-values
Chien Y *et al.* 2018[152]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	Yes Quantitative measure for outcomes: - Of 15 patients evaluated 2 years post-treatment, 5 gained full head control (P < 0.0001); 4 could sit unassisted (P = 0.0004); and 1 could stand with support - Of 7 patients evaluated 5 years post-treatment, 4 gained full head control and the ability to sit	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	Yes - Of 15 patients evaluated 2 years post-treatment, 5 gained full head control (P < 0.0001); 4 could sit unassisted (P = 0.0004); and 1 could stand with support - Of 7 patients evaluated 5 years post-treatment, 4 gained full head control and the ability to sit unassisted (P < 0.0001 each); 2 could stand with

			unassisted (P < 0.0001 each); 2 could stand with support (P = 0.0054)				support (P = 0.0054)
Paul Wuh-liang Hwu *et al.* 2021 (NCT01395641, NCT02926066)[40]	Yes. Parents or guardians agreed to cooperate and signed informed consent	NA No information available on exposure accurately measured to minimise bias	No Quantitative measure for outcomes for PDMS-2 and AIMS	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
Chien Y H *et al.* 2018[151]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Quantitative measure for outcomes: - All patients had sustained de novo dopamine production - Of 15 patients evaluated 2 years post-treatment, 5 gained full head control (P < 0.0001); 4 could sit unassisted (P = 0.0004); and 1 could stand with support - Of 7 patients evaluated 5 years post-treatment, 4 gained full head control and the ability to sit unassisted (P < 0.0001 each); 2 could stand with support (P = 0.0054)	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 2 - 5 years	Yes - Of 15 patients evaluated 2 years post-treatment, 5 gained full head control (P < 0.0001); 4 could sit unassisted (P = 0.0004); and 1 could stand with support - Of 7 patients evaluated 5 years post-treatment, 4 gained full head control and the ability to sit unassisted (P < 0.0001 each); 2 could stand with support (P = 0.0054)

Ni-Chung Lee *et al.* 2018[153]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Quantitative measure for outcomes: - 5/15 gain full head control (p<0.0001), 4/15 gain sitting unassisted (p=0.0004), and one subject achieved standing with support at 2 years. - At five years, 4/7 gain full head control and sit unassisted (p<0.0001), and 2/7 stand with support (p=0.0054) - One additional patient is able to take steps holding an examiner's hand - One patient is walking independently	NA No information available on authors identified all important confounding factors NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 2 - 5 years	- 5/15 gain full head control (p<0.0001), 4/15 gain sitting unassisted (p=0.0004), and one subject achieved standing with support at 2 years. - At five years, 4/7 gain full head control and sit unassisted (p<0.0001), and 2/7 stand with support (p=0.0054) - One additional patient is able to take steps holding an examiner's hand - One patient is walking independently
Yin-Hsiu Chien *et al.* 2017[34] (NCT01395641)	Yes. We enrolled and recruited patients only by referral from doctors or families with AADC. We enrolled and recruited patients only by referral from doctors or families with AADC.	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 12 months	NA No information available in terms of confidence interval and p-values
Paul Wuh-liang Hwu *et al.* 2021[142]	Yes. Parents or guardians agreed to	NA No information available on	NA No information available on the	NA No information available on authors	NA No information available on authors	Yes Follow-up period = 12 months	NA No information available in terms of

(NCT01395641, NCT02926066)	cooperate and signed informed consent	exposure accurately measured to minimise bias	outcome accurately measured to minimise bias	identified all important confounding factors	taken account of the confounding factors in the design and/or analysis		confidence interval and p-values
Paul Wuh-liang Hwu *et al.* 2021[139] (NCT01395641, NCT02926066)	Yes. Parents or guardians agreed to cooperate and signed informed consent	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 12 months	NA No information available in terms of confidence interval and p-values
Krystof Bankiewicz *et al.* 2018[77]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Qualitative measure for outcomes: Improvement in motor function, cognitive function, F-DOPA PET still exhibited signals of AADC activity over the putamens	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 12 months	NA No information available in terms of confidence interval and p-values
Ni-Chung Lee *et al.* 2017[155]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up period = 12 months	NA No information available in terms of confidence interval and p-values
Wuh-Liang Hwu *et al.* 2017[154]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	No Qualitative measure for outcomes: Improvement in motor function, cognitive function, F-DOPA PET still exhibited signals of AADC activity over the putamens	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Motor development and cognitive function showed improvement over this 5-year period, with the most substantial gains observed during the first two years after gene transduction	NA No information available in terms of confidence interval and p-values
Wuh-Liang Hwu *et al.* 2015[156]	NA	NA	NA	NA	NA	Yes	NA

	No information available on cohort recruitment	No information available on exposure accurately measured to minimise bias	No information available on the outcome accurately measured to minimise bias	No information available on authors identified all important confounding factors	No information available on authors taken account of the confounding factors in the design and/or analysis	The mean follow-up period = 3.8 years (3-4.5 years)	No information available in terms of confidence interval and p-values
K-Y Chan *et al.* 2012[79]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
K. Bankiewicz *et al.* 2019[75]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes All subjects achieved recognizable gains in head control and voluntary movement at 6-18 months. All children developed mild to moderate involuntary movements (dyskinesia) that peaked in severity 1-2 months after surgery and then improved.	NA No information available in terms of confidence interval and p-values
Toni S. Pearson *et al.* 2020[7]	Yes. Created a written questionnaire to collect data about disease onset, symptom course, developmental outcome, and mortality (see Supporting Information). Participants were	NA No information available on exposure accurately measured to minimise bias	No Qualitative measure for outcomes: Improvements in tone or spontaneous movements, improved alertness, and decreased oculogyric crises	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	Yes Dystonic episodes with symptoms limited to the head and neck (median age 10.4, range 4.3-26.1 years) (Z = 2.232, P = .026)

	recruited via two sources: (1) The International Working Group of Neurotransmitter-Related Disorders (iNTD) patient registry, which includes collaborating physicians from 32 centres in North America, Europe, and Asia13; and (2) The AADC Research Trust, a parent-run foundation based in the United Kingdom.						
Tai *et al.*, 2022[157]	Yes Recruited from 3 clinical trials (AADC-CU/1601, AADC-010, AADC-011)	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	Yes Follow-up for at least 1 year and up to 5 years	Yes P-values given for statistically significant change in results
Bergkvist *et al.*, 2021[8]	Yes Systematic review of natural history of patients with AADC deficiency	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
Boenkhe *et al.*, 2021[158]	Yes A directed literature seach	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values

					in the design and/or analysis		
Boenkhe *et al.*, 2021[159]	NA No information available on cohort recruitment	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
Havali *et al.*, 2021[83]	Yes Patient with diagnosed AADC deficiency recruited	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
Ling *et al.*, 2021[160]	Yes Retrospective review of confirmed diagnoses of AADC deficiency	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values
Saberian *et al.*, 2021[112]	Yes Physicians experienced in the management of patients with AADC-deficiency were asked to complete the questionnaire based on the information available in medical records	NA No information available on exposure accurately measured to minimise bias	NA No information available on the outcome accurately measured to minimise bias	NA No information available on authors identified all important confounding factors	NA No information available on authors taken account of the confounding factors in the design and/or analysis	NA No information available on follow-up of patients	NA No information available in terms of confidence interval and p-values

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; AIMS – Abnormal Involuntary Movement Scale; CI – Confidence intervals CSF – Cerebrospinal fluid; HVA – Homovanillic acid; iNTD – The International Working Group of Neurotransmitter-Related Disorders; IQR – Interquartile range; NA – Not available; OGC – Oculogyric crisis; PDMS-2 – Peabody Developmental Motor Scale, Second Edition; PET – Positron emission tomography

D1.4 Critical appraisal of relevant clinical evidence

Table 105: AADC-CU/1601: Critical appraisal[16]

Study name: AADC-CU/1601: Compassionate use treatment with eladocagene exuparvovec patients with AADC deficiency		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	As per clinical trial requirements, set inclusion and exclusion criteria, described in the publication and protocol, were followed.
Was the exposure accurately measured to minimise bias?	Yes	All 8 patients (100%) received eladocagene exuparvovec treatment. Full details of interventions and follow-ups are provided.
Was the outcome accurately measured to minimise bias?	Yes	• All patients (100%) followed-up for primary outcomes up to month 24, 75% followed-up at month 60 and 25% followed-up post 60-months. • Follow-ups for all patients were conducted at voluntary monthly sessions, though a sequential gatekeeping procedure was used for testing at the 60-month timepoint. • Primary outcomes (PDMS-2) and secondary outcomes (AIMS, CDIIT, neurological examinations and pharmacodynamic endpoints) were measured consistently in line with the guidelines set out in the CSR.
Have the authors identified all important confounding factors?	Yes	All major influences on outcomes included: baseline characteristics and (age at baseline, PDMS-2 baseline scores, AIMS baseline scores).
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The primary analysis of efficacy does not involve any covariate adjustments. For the secondary endpoint analyses of PDMS-2, AIMS, and CDIIT, the repeated measures models included the covariates of baseline scores, age at the time of eladocagene exuparvovec infusion, and visit.
Was the follow-up of patients complete?	Yes	All 8 patients (100%) completed the follow-up at 24 months. 6 patients (75%) completed the follow-up at month 60.
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	95% confidence intervals used, and P-values provided for primary and secondary endpoints.

Abbreviations: AADC - Aromatic L-amino acid decarboxylase; CASP – Critical appraisal skills programme

Source: Clinical study report for AADC-CU/1601

Table 106: AADC-010 - Critical appraisal of observational studies[18]

Study name: AADC-010: A phase 1/2 clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	As per clinical trial requirements, set inclusion and exclusion criteria, described in the publication and protocol, were followed. The demographic and baseline characteristics of the study population were representative of patients with AADC deficiency and clinically consistent with the natural history control group.
Was the exposure accurately measured to minimise bias?	Yes	All 10 patients (100%) received eladocagene exuparvovec treatment. Full details of interventions and follow-ups are provided.
Was the outcome accurately measured to minimise bias?	Yes	• All patients (100%) followed-up for primary outcomes up to month 12, 90% followed-up to month 24, 80% followed-up to month 36, with 50% continuing post 60-months. • Follow-ups for all patients were conducted at equivalent three-monthly sessions for the first year, with voluntary ups every 6-months thereafter. A sequential gatekeeping procedure was used for testing at the 24-month timepoint. • Primary outcomes (PDMS-2) and secondary outcomes (AIMS, Bayley-III, body weight, immunogenicity endpoints and pharmacodynamic endpoints) were measured consistently in line with the guidelines set out in the CSR.
Have the authors identified all important confounding factors?	Yes	All major influences on outcomes included: baseline characteristics and demographics (age at baseline, PDMS-2 baseline scores, AIMS baseline scores, Bayley-III baseline scores).
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The primary analysis of efficacy did not involve any adjustments for covariates. For the secondary endpoint analyses of motor development (PDMS-2, AIMS, and Bayley-III), the repeated measures models incorporated various covariates, such as baseline scores, age at the time of eladocagene exuparvovec gene-replacement therapy, and visit.
Was the follow-up of patients complete?	Yes	All 10 patients (100%) completed the follow-up at 12 months.
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	95% confidence intervals used, and P-values provided for primary and secondary endpoints.

Abbreviations: AADC - Aromatic L-amino acid decarboxylase; CASP – Critical appraisal skills programme
Source: Clinical study report for AADC-010

Table 107: AADC-011 - Critical appraisal of observational studies[17]

Study name: AADC-011: A clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC - an expansion		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	As per clinical trial requirements, set inclusion and exclusion criteria, described in the publication and protocol, were followed. The demographic and baseline characteristics of the study population were representative of patients with AADC deficiency and clinically consistent with the natural history control group.
Was the exposure accurately measured to minimise bias?	Yes	All 12 patients (100%) received eladocagene exuparvovec treatment. Full details of interventions and follow-ups are provided.
Was the outcome accurately measured to minimise bias?	Yes	• The mean follow-up for primary outcomes was 11.1 months. • Follow-ups for all patients were conducted at equivalent three-monthly sessions for the first year, with a voluntary enrolment to a follow-up study thereafter. • Primary outcomes (PDMS-2) and secondary outcomes (PDMS-2, AIMS, Bayley-III) were measured consistently in line with the guidelines set out in the CSR.
Have the authors identified all important confounding factors?	Yes	All major influences on outcomes included: baseline characteristics and demographics (age at baseline, PDMS-2 baseline scores, AIMS baseline scores, Bayley-III baseline scores).
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The primary analysis of efficacy does not involve any covariate adjustments. For the secondary endpoint analyses of PDMS-2, AIMS, and Bayley, repeated measures models included the covariates of baseline scores, age at the time of eladocagene exuparvovec infusion, and visit.
Was the follow-up of patients complete?	Yes	9 of the 12 patients (75.0%) completed the follow-up at 12 months.
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	95% confidence intervals used, and P-values provided for primary and secondary endpoints.

Abbreviations: AADC - Aromatic L-amino acid decarboxylase; CASP – Critical appraisal skills programme

Source: Clinical study report for AADC-011

Appendix E: Subgroup analysis

No subgroup analyses were performed in any of the three individual studies supporting eladocagene exuparvovec.

Appendix F: Adverse reactions

All information pertaining to adverse reactions has been included in the Section B.2.10.

Appendix G: Published cost-effectiveness studies

G1.1 Search strategy

For the SLR of published cost-effectiveness studies, the following databases were searched: Embase (covers biomedical literature from 1974 to present), MEDLINE (covers journals from 1966 to present), Embase Classic (the Embase back file covering citations between 1947 and 1973).

Supplementary searches of "grey" literature were performed using set search terms in Google Scholar, NICE website, Pharmaceutical Benefits Advisory Committee (PBAC) website, Canadian Agency for Drugs and Technologies in Health (CADTH) website, Scottish Medicines Consortium (SMC) website and Institute for Clinical and Economic Review (ICER) website.

Furthermore, searches included clinicaltrials.gov, the manufacturer's repository of evidence, websites of manufacturers of comparator products, and bibliographic searching of any SLRs identified during screening. The following relevant congresses were also searched with a date restriction, where possible, over the last three years (2019–2022): The Professional Society for Health Economics and Outcomes Research (ISPOR) conference proceedings (EU), ISPOR conference proceedings (US), European Paediatric Neurology Society, Society for the Study of Inborn Errors of Metabolism, International Congress of Inborn Errors of Metabolism, British Paediatric Neurology Association, World Orphan Drug Congress, European Society for Gene and Cell Therapy, American Society of Gene and Cell Therapy, Gene Therapy for Neurological Disorders (US/EU).

Table 108: Embase, MEDLINE and Embase Classic (Embase index terms used as all databases were searched within the Embase interface) [date searched: 23rd February 2022]

Description	Search terms	Hits
Population	'aromatic amino acid decarboxylase deficiency'/exp OR 'aadc gene' OR 'AADC-deficiency' OR 'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR 'aadc-d' OR 'dopa decarboxylase deficiency' OR 'ddc gene' OR 'ddc deficiency' OR 'aadc-d' OR 'aadc varian*' OR 'aadc syndrom*' OR 'aadc disease' OR 'aadc disorder'	551
Interventions/ comparators	'Upstaza' OR 'AAV2 NEAR/2 hAADC' OR 'adeno-associated virus adj8 human AADC' OR 'eladocagene exuparvovec' OR 'AGIL NEAR/2 AADC'	50

Description	Search terms	Hits
Study types: RCT Filter	('clinical trial'/de OR 'randomised controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomisation'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	2,480,623
Observation study filter	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomised controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow-up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross-sectional' NEXT/1 (study OR studies)):ti,ab)	3,941,832
Combine filters and restrict date	#1 OR #2 AND (#3 OR #4) AND [humans]/lim	113
Economic Filter	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,037,062
Quality-of-life filter[134] (https://abstracts.cochrane.org/2015-vienna/ sensitivity-search-filter-designed-identify-studies-reporting-health-state-utility)	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR (caregiver OR carer)	1,194,398
Resource use filter	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR	2,041,276

Description	Search terms	Hits
	hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti) OR (carer OR carers OR caregiver OR caregivers)	
Combine terms and restrict date	#1 AND (#6 OR #7 OR #8) AND [humans]/lim	35
Combine terms	#5 OR #9	142

Abbreviations: RCT – Randomized control trial

Table 109: CENTRAL and Cochrane Clinical Answers (Cochrane Library interface) [date searched: 23rd February 2022]

Clinical search strategy		
Description	**Search terms**	**Hits**
Terms for population	"aromatic amino acid decarboxylase deficiency" OR "aadc gene" OR "AADC-deficiency" OR "aromatic amino acid decarboxylase deficiency" OR "aromatic L-amino acid decarboxylase deficiency" OR "aadc-d" OR "dopa decarboxylase deficiency" OR "ddc gene" OR "ddc deficiency" OR "aadc-d"	2
MeSH terms for population	MeSH descriptor [aromatic L-amino acid decarboxylase] explode all trees	11
Interventions/comparators	“Upstaza” OR “AAV2” NEAR/2 “hAADC” OR “adeno-associated virus” adj8 “human AADC” OR “eladocagene exuparvovec” OR “AGIL” NEAR/2 “AADC”	0
Combine terms	#1 OR #2 OR #3 in trials	12

Abbreviations: MeSH – Medical subject heading

Table 110: ScHARRHUD search strategy [date searched: 23rd February 2022]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc-d’ OR ‘AADC-deficiency’	0

Abbreviations: HRQoL – Health-related quality-of-life; ScHARRHUD - School of health and related research, University of Sheffield

Table 111: EuroQoL database search strategy [date searched: 23rd February 2022]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc-d’ OR ‘AADC-deficiency’	0

Abbreviations: HRQoL – Health-related quality-of-life

Table 112: NHS HTA and EED search strategy (via University of York website) [date searched: 23rd February 2022]

CRD HTA and EED database - Cost-effectiveness, cost and resource use and quality-of-life search strategy		
Description	**Search terms**	**Hits**
Terms for population	aromatic amino acid decarboxylase deficiency OR aromatic L-amino acid decarboxylase deficiency OR aadc-d OR aadc-d OR AADC-deficiency	0
Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	25,686
Combine filters	#1 AND #2 in NHSEED, HTA	0
QoL filter	qol OR quality-of-life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	13,073
Combine terms	#1 AND #4 in NHSEED, HTA	0

Abbreviations: CRD – Centre for reviews and dissemination; EED – Economic evaluation database; HTA – Health technology assessment; NHS – National health service; QoL – Quality-of-life

G1.2 Study selection

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified publications based on title and abstract (first pass) for inclusion using the review question and selection criteria. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in line with NICE guidelines.

Following the completion of first pass, full text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria by two independent reviewers. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in alignment with NICE guidance.

G1.3 Data extraction

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers or by consulting a third reviewer if necessary. For each publication, data were extracted into a data collection form (Excel based with tables suitably formatted to align with NICE 2022 SLR template) and developed in line with the University of York CRD and NICE reporting requirements.[135,136]

For any cost-effectiveness publications that were found, a quality assessment of these cost-effectiveness publications was conducted using the Drummond and Jefferson criteria[137].

G1.4 Selection criteria

Table 113: Selection criteria for cost-effectiveness publications

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with AADC-deficiency	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	Any intervention/comparator (i.e. no restriction)	No intervention / comparators of interest
Outcomes	Cost per QALY gained Cost per life-year gained	No reported outcomes of interest, i.e., budget impact model outcomes
Study type	Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • EEACT	Burden of disease study Resource use study Budget impact study
Publication type	Article, conference abstract, conference paper, article in press	Short survey Reviews Letters Comment articles
Language	English	Non-English

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; EEACT – Economic evaluation alongside clinical trials; QALY – Quality-adjusted life-year; SLR – Systematic literature review

Please refer to Appendix D: Identification, selection and synthesis of clinical evidence for all publications excluded at the first and second pass stages, with reasons for justification provided for those excluded at the second pass stage. Please see Table 114 for a summary of the cost-effectiveness publication identified as part of the SLR.

G1.5 Search results

Of the 166 publications identified across the SLR for title and abstract screening, 4 were considered for full text review of review question 2: cost-effectiveness publications.

Following review of the full texts, 3 publications were excluded because they did not meet the selection criteria: 2 did not meet the outcomes criteria, and 1 was unavailable. A grey literature search provided no additional cost-effectiveness studies which met the inclusion criteria. Overall, 1 publication met the selection criteria following the first and second pass of the cost-effectiveness studies review and was extracted. Studies included in first pass but not extracted are presented in Table 114.

The SLR retrieved 1 publication available as an abstract (Simons *et al.,* 2022[88]), reporting a cost-effectiveness analysis of a gene therapy for patients with AADC deficiency.

Table 114: Summary of cost-effectiveness publications (n=1)

Reference	Region, currency	Perspective	Population and intervention	Time horizon	Outcomes/results
Simons *et al.,* 2022[88] *POSC107 Long Term Outcomes for Patients with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: A Modelling Study Exploring the Benefit of Gene Therapy*	UK perspective (NHS), GBP	NHS and social services	Patients with AADC deficiency, on BSC	Lifetime horizon	QALYs 17.30 undiscounted QALYs

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; BSC – Best supportive care; GBP – Great British Pounds; NHS – National Health Service; QALY – Quality-adjusted life year; UK – United Kingdom

Appendix H: Health-related quality-of-life studies

H1.1 Search strategy

For the SLR, the following databases were searched: Embase (covers biomedical literature from 1974 to present), MEDLINE (covers journals from 1966 to present), Embase Classic (the Embase back file covering citations between 1947 and 1973).

Supplementary searches of "grey" literature were performed using set search terms in Google Scholar, NICE website, Pharmaceutical Benefits Advisory Committee (PBAC) website, Canadian Agency for Drugs and Technologies in Health (CADTH) website, Scottish Medicines Consortium (SMC) website and Institute for Clinical and Economic Review (ICER) website.

Furthermore, searches included clinicaltrials.gov, the manufacturer's repository of evidence, websites of manufacturers of comparator products, and bibliographic searching of any SLRs identified during screening. The following relevant congresses were also searched with a date restriction, where possible, over the last three years (2019–2022): The Professional Society for Health Economics and Outcomes Research (ISPOR) conference proceedings (EU), ISPOR conference proceedings (US), European Paediatric Neurology Society, Society for the Study of Inborn Errors of Metabolism, International Congress of Inborn Errors of Metabolism, British Paediatric Neurology Association., World Orphan Drug Congress, European Society for Gene and Cell Therapy, American Society of Gene and Cell Therapy, Gene Therapy for Neurological Disorders (US/EU).

Table 115: Embase, MEDLINE and Embase Classic (Embase index terms used as all databases were searched within the Embase interface) [date searched: 23rd February 2022]

Description	Search terms	Hits
Population	'aromatic amino acid decarboxylase deficiency'/exp OR 'aadc gene' OR 'AADC-deficiency' OR 'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR 'aadc-d' OR 'dopa decarboxylase deficiency' OR 'ddc gene' OR 'ddc deficiency' OR 'aadc-d' OR 'aadc varian*' OR 'aadc syndrom*' OR 'aadc disease' OR 'aadc disorder'	551
Interventions/ comparators	'Upstaza' OR 'AAV2 NEAR/2 hAADC' OR 'adeno-associated virus adj8 human AADC' OR 'eladocagene exuparvovec' OR 'AGIL NEAR/2 AADC'	50
Study types: RCT Filter	('clinical trial'/de OR 'randomised controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomisation'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	2,480,623

Description	Search terms	Hits
Observation study filter	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomised controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow-up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross-sectional' NEXT/1 (study OR studies)):ti,ab)	3,941,832
Combine filters and restrict date	#1 OR #2 AND (#3 OR #4) AND [humans]/lim	113
Economic Filter	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,037,062
Quality-of-life filter[134] (https://abstracts.cochrane.org/2015-vienna/ sensitivity-search-filter-designed-identify-studies-reporting-health-state-utility)	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR (caregiver OR carer)	1,194,398
Resource use filter	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti) OR (carer OR carers OR caregiver OR caregivers)	2,041,276
Combine terms and restrict date	#1 AND (#6 OR #7 OR #8) AND [humans]/lim	35

Description	Search terms	Hits
Combine terms	#5 OR #9	142

Abbreviations: RCT – Randomized control trial

Table 116: CENTRAL and Cochrane Searching (Cochrane Library interface) [date searched: 23rd February 2022]

Clinical search strategy		
Description	**Search terms**	**Hits**
Terms for population	"aromatic amino acid decarboxylase deficiency" OR "aadc gene" OR "AADC-deficiency" OR "aromatic amino acid decarboxylase deficiency" OR "aromatic L-amino acid decarboxylase deficiency" OR "aadc-d" OR "dopa decarboxylase deficiency" OR "ddc gene" OR "ddc deficiency" OR "aadc-d"	2
MeSH terms for population	MeSH descriptor [aromatic L-amino acid decarboxylase] explode all trees	11
Interventions/comparators	“Upstaza” OR “AAV2” NEAR/2 “hAADC” OR “adeno-associated virus” adj8 “human AADC” OR “eladocagene exuparvovec” OR “AGIL” NEAR/2 “AADC”	0
Combine terms	#1 OR #2 OR #3 in trials	12

Abbreviations: MeSH – Medical subject heading

Table 117: ScHARRHUD search strategy [date searched: 23rd February 2022]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc-d’ OR ‘AADC-deficiency’	0

Abbreviations: HRQoL – Health-related quality-of-life; ScHARRHUD - School of health and related research, University of Sheffield

Table 118: EuroQoL database search strategy [date searched: 23rd February 2022]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc-d’ OR ‘AADC-deficiency’	0

Abbreviations: HRQoL – Health-related quality-of-life

Table 119: NHS HTA and EED search strategy (via University of York website) [date searched: 23rd February 2022]

CRD HTA and EED database - Cost-effectiveness, cost and resource use and quality-of-life search strategy		
Description	**Search terms**	**Hits**
Terms for population	aromatic amino acid decarboxylase deficiency OR aromatic L-amino acid decarboxylase deficiency OR aadc-d OR aadc-d OR AADC-deficiency	0
Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	25,686
Combine filters	#1 AND #2 in NHSEED, HTA	0
QoL filter	qol OR quality-of-life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	13,073
Combine terms	#1 AND #4 in NHSEED, HTA	0

Abbreviations: CRD – Centre for reviews and dissemination; EED – Economic evaluation database; HTA – Health technology assessment; NHS – National health service; QoL – Quality-of-life

H1.2 Study selection

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified publications based on title and abstract (first pass) for inclusion using the review question and selection criteria. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in line with NICE guidelines.

Following the completion of first pass, full text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria by two independent reviewers. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in alignment with NICE guidance.

H1.3 Data extraction

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers or by consulting a third reviewer if necessary. For each publication, data were extracted into a data collection form (Excel based with tables suitably formatted to align with NICE 2022 SLR template) and developed in line with the University of York CRD and NICE reporting requirements.[135,136] A quality assessment of cost-effectiveness publications was conducted using the Drummond and Jefferson criteria.[137]

H1.4 Selection criteria

Table 120:Selection criteria for health-related quality-of-life studies

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with AADC-deficiency Caregivers of patients with AADC-deficiency	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	No restriction on intervention/comparator	No intervention / comparators of interest
Outcomes	Utilities Disutilities HRQoL measures (i.e. no restriction)	No reported outcomes of interest
Study type	RCTs Non-RCTs Observational studies HRQoL elicitation studies HRQoL validation studies Economic evaluations: o Cost-utility analysis o EEACT	Individual case study reports
Publication type	Article, conference abstract, conference paper, article in press	Short survey Reviews Letters Comment articles
Language	English	Non-English

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; EEACT – Economic evaluation alongside clinical trials; HRQoL – Health-related quality-of-life; RCT – Randomised controlled trials; SLR – Systematic literature review

Please refer to Appendix D: Identification, selection and synthesis of clinical evidence for all publications excluded at the first and second pass stages, with reasons for justification provided for those excluded at the second pass stage. Please see Table 121 for a summary of the HRQoL publications identified as part of the SLR.

Table 121: Summary of HRQoL publications (n=9)

Reference	N	Population	Intervention	Utilities
Smith *et al.,* 2021[164] *Eliciting health state utilities for Aromatic L-amino Acid Decarboxylase (AADC) defciency: a UK vignette study*	A total of 1,598 participants completed the vignettes	The vignettes were completed online by panel participants drawn from a representative sample of the United Kingdom residential population.	NR	The mean health-state utilities (standard deviation) for the TTO task were: bedridden state 0.49 (0.34), head control 0.54 (0.33), sitting unsupported 0.63 (0.31), standing with assistance 0.68 (0.31), walking with assistance 0.73 (0.31). For the SG, mean health state utilities were: bedridden state 0.56 (0.28), head control 0.57 (0.27), sitting unsupported 0.67 (0.24), standing with assistance 0.70 (0.24), walking with assistance 0.75 (0.25).
Smith *et al.,* 2021[126] *A Discrete Choice Experiment to Derive Health Utilities for Aromatic L-amino Acid Decarboxylase (AADC) Deficiency in France*	Completed online by 1,001 participants	A representative sample of the French general population was recruited.	NR	The rescaled utilities ranged from 0.3891 to 0.5577 (difference of 0.17 utilities) for TTO anchors corresponding to the worst and best health states. Health utilities ranged from 0.5534 to 0.7093 for the SG anchors. The disutility associated with a transition from “no problems walking” to “bedridden” was −0.0533, whereas disutility of moving from “constant screaming” relative to “no screaming” was −0.0248. The disutility associated with daily OCG was −0.0167.
Buesch *et al.*, 2021[165] *Utilities in a rare disease collected via vignettes in general population samples from the UK and France: comparison of results.*	UK, n=1,598 France, n=1,001	Participants completed vignette studies in the UK and France	NR	Mean health utilities (standard deviation) presented below- TTO results for congruent UK responses were: bedridden 0.42 (±0.32), head control 0.48 (±0.32), sitting unsupported 0.58 (±0.31), standing with assistance 0.63 (±0.32), walking with assistance 0.67 (±0.33). For France respective utilities were: bedridden 0.39 (±0.36), head control 0.48 (±0.36), sitting unsupported 0.53 (±0.37), standing with assistance 0.53 (±0.38), walking with assistance 0.56 (±0.38).

Smith *et al.*, 2021(a)[166] *Capturing the health-related quality-of-life of children living with AADC deficiency through a vignette study: a French experience.*	1,001	Panel participants from a French representative sample	NR	The mean TTO health utilities (n=729) were: 0.3891 (bedridden state), 0.4839 (head control), 0.5271 (sitting unsupported), 0.5293 (standing with assistance), and 0.5577 (walking with assistance). The SG utilities (n=664) ranged from 0.5534 for bedridden to 0.7093 for walking with assistance.
Smith *et al.*, 2021(b).[126] *A discrete choice experiment to derive health state utilities for aromatic L-amino acid decarboxylase (AADC) deficiency in france.*	1,001	Participants from a representative sample of the French general population	NR	The mean health states utilities were 0.389 for the bedridden state, 0.432 head control, 0.489 sitting unsupported, 0.526 standing with assistance, and 0.558 walking with assistance. The disutility from “walking with assistance” to “bedridden” was -0.0533. The disutility of “constant screaming” to “no screaming” was -0.0248. The disutility of daily OGC was -0.0167.
Smith *et al.*, 2021(c).[164] *Eliciting Health State Utilities for Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: A Vignette Study in France*	TTO=729, SG=664	Respondents were recruited from a panel maintained by a third party (Qualtrics, Provo, USA). The sample was selected to be representative of the adult population in France.	NR	**TTO Congruent** HUI3 Values, Attribute/ Mean (SD): Vision=0.9509 (0.0794) Hearing=0.9342 (0.1071) Speech=0.9305 (0.0965) Cognition=0.8953 (0.1342) Ambulation=0.9277 (0.0929) Dexterity=0.9399 (0.0873) Emotion=0.9511 (0.0529) Pain=0.9553 (0.0409) Global HUI3=0.5263 (0.4123) Mean Health State Utilities, Mean Utilities (SD): Bedridden=0.3891 (0.3624) Head Control=0.4839 (0.3573) Sitting=0.5271 (0.3651) Standing=0.5293 (0.3749) Walking=0.5577 (0.3789)

				Mean Health State Utilities by Gender - Female, Mean (SD): Bedridden=0.3627 (0.3692) Head Control=0.4670 (0.3709) Sitting=0.5118 (0.3815) Standing=0.5042 (0.3909) Walking=0.5366 (0.4000) Mean Health State Utilities by Gender - Male, Mean (SD): Bedridden=0.4188 (0.3527) Head Control=0.5028 (0.3409) Sitting=0.5443 (0.3456) Standing=0.5575 (0.3546) Walking=0.5816 (0.3526) **SG Congruent** HUI3 Values, Attribute/ Mean (SD): Vision=0.9461 (0.0834) Hearing=0.9281 (0.1117) Speech=0.9261 (0.0979) Cognition=0.8855 (0.139) Ambulation=0.9212 (0.0965) Dexterity=0.932 (0.0922) Emotion=0.9493 (0.052) Pain=0.9523 (0.0413) Global HUI3=0.4924 (0.4198) Mean Health State Utilities, Mean Utilities (SD): Bedridden=0.5534 (0.3024) Head Control=0.6209 (0.2865) Sitting=0.6755 (0.2723) Standing=0.679 (0.2791) Walking=0.7093 (0.2712) Mean Health State Utilities by Gender - Female, Mean (SD): Bedridden=0.5689 (0.3137) Head Control=0.6408 (0.3015) Sitting=0.7046 (0.2781) Standing=0.7095 (0.2842)

				Walking=0.7388 (0.2752) Mean Health State Utilities by Gender - Male, Mean (SD): Bedridden=0.5375 (0.2900) Head Control=0.6005 (0.2692) Sitting=0.6458 (0.2634) Standing=0.6476 (0.2707) Walking=0.6791 (0.2639)
Smith *et al.*, 2020(a).[131] *A discrete choice experiment to derive health state utilities for aromatic L-amino acid decarboxylase (AADC) deficiency in the United Kingdom*	1,596	Panel participants from a UK representative sample	NR	Worst health state: 0.4217 Best health state: 0.6703
Smith *et al.*, 2020(b)[167] *A vignette study to derive health state utilities for aromatic L-amino acid decarboxylase (AADC) deficiency in the United Kingdom (UK)*	1,596	Panel participants drawn from a representative sample of the United Kingdom population	NR	Mean health utilities (standard deviation) for the TTO were: bedridden state 0.42 (60.32), head control 0.48 (60.32), sitting unsupported 0.58 (60.31), standing with assistance 0.63 (60.32), walking with assistance 0.67 (60.33). For the SG, mean utilities (standard deviation) were: bedridden state 0.58 (60.27), head control 0.59 (60.27), sitting unsupported 0.69 (60.24), standing with assistance 0.73 (60.22), walking with assistance 0.79 (60.20) Females had higher utility values compared to males (range: 0.44 to 0.69; 0.39 to 0.64, respectively)
Smith *et al.*, 2021[168] *A discrete choice experiment to derive health utilities for aromatic L-amino Acid Decarboxylase (AADC) deficiency*	1,596	NR	NR	From the vignette study, the estimated TTO utility weights for the best and worst health states were 0.7279 and 0.494, respectively.

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; HRQoL – Health-related quality-of-life; NR – Not reported; OGC – Oculogyric crisis; QALY – Quality-adjusted life year; SG – Standard gamble; TTO – Time-trade off; UK – United Kingdom; US – United States.

H1.5 Search results

Of the 166 publications identified across the SLR for title and abstract screening, 21 were considered for full text review of review question 3: HRQoL publications.

Following review of the full texts, 15 publications were excluded because they did not meet the selection criteria: 1 did not meet the population criteria, 13 did not meet the outcomes criteria, and 1 was unavailable. A grey literature search provided an additional 3 quality-of-life publications which met the inclusion criteria. Overall, 9 publications met the selection criteria following the first and second pass of the HRQoL studies review and were extracted. Information on the links between publications and posters is displayed in Table 122.

No publications identified in this SLR reported EQ-5D data in patients with AADC deficiency. Deriving health utilities for ultra-rare medical conditions such as AADC deficiency poses challenges. The severity and rarity of AADC deficiency, combined with the young age of patients, mean that robust utility values can be difficult to derive from patients or parents/caregivers. Alternative methods to well-established utility instruments (e.g. EQ-5D) may be used to generate utilities (e.g., vignettes, discrete choice experiments (DCE) or direct valuation of a health state using standard gamble or time trade-off).[111]

Table 122: Publication and poster links

Category	Topic	Main publication	Associated abstracts
	Methodology	**Hanbury 2021**[56] Andria Hanbury, Adam B Smith, Katharina Buesch. Deriving Vignettes for the Rare Disease AADC Deficiency Using Parent, Caregiver and Clinician Interviews to Evaluate the Impact on Health-Related Quality-of-life. Patient Relat Outcome Meas. 2021 Jan 7;12:1-12. doi: 10.2147/PROM.S278258. eCollection 2021.	None
HRQoL	**UK vignette study**	**Smith 2021**[164] Eliciting health state utilities for Aromatic L-amino Acid Decarboxylase (AADC) deficiency: a UK vignette study. Patient Rep Outcomes. 2021 Dec 11;5(1):130. doi: 10.1186/s41687-021-00403-0	**Smith 2020**[167] Smith, A., Hanbury, A. & Buesch, K. A vignette study to derive health state utilities for aromatic L-amino acid decarboxylase (aadc) deficiency in the United Kingdom (UK). Value in Health (2020) **Comparison of France vs UK** Buesch, K. et al.[165] Utilities in a rare disease collected via vignettes in general population samples from the UK and France: comparison of results. Value in Health (2021).
	UK DCE	**Smith 2021**[168] Smith, A. B., Hanbury, A., Whitty, J. A. & Buesch, K. A	**Smith 2020**[131] Smith, A., Hanbury, A., Whitty, J. & Buesch, K. A DISCRETE CHOICE

		Discrete Choice Experiment to Derive Health Utilities for Aromatic L-amino Acid Decarboxylase (AADC) Deficiency. PROM Volume 12, 97–106 (2021).	EXPERIMENT TO DERIVE HEALTH STATE UTILITIES FOR AROMATIC L-AMINO ACID DECARBOXYLASE (AADC) DEFICIENCY IN THE UNITED KINGDOM. Value in Health (2020).
	French vignette study	**Smith 2021**[164] Smith, A. B. et al. Eliciting Health State Utilities for Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: A Vignette Study in France. PROM Volume 12, 237–246 (2021).	**Smith 2021**[166] Smith, A. et al. Capturing the health-related quality-of-life of children living with aadc deficiency through a vignette study: a French experience. Value in Health (2021). **Comparison of France vs UK** Buesch, K. et al. [165] Utilities in a rare disease collected via vignettes in general population samples from the UK and France: comparison of results. Value in Health (2021).
	French DCE	**Smith 2022**[126] Smith, Hanbury, Whitty, Beitia Ortiz de Zarate, Hammes, Pouvourville, Buesch. A Discrete Choice Experiment to Derive Health Utilities for Aromatic L-amino Acid Decarboxylase (AADC) Deficiency in France. Patient Related Outcome Measures. 2022 Jan 25;13:21-30. doi: 10.2147/PROM. S332519. eCollection 2022	**Smith 2021**[126] Smith, A. et al. A discrete choice experiment to derive health state utilities for aromatic L-amino acid decarboxylase (aadc) deficiency in france. Value in Health (2021)
	EQ-5D	*There is a Williams manuscript currently in peer review*	**Williams 2021** [169] Willams, K., Skrobanski, H., Buesch, K. & Acaster, S. Measuring carer utility in rare paediatric disease: a mixed methods case study in aromatic L-amino acid decarboxylase deficiency (AADCd). (2021).
	Qualitative QoL	**Williams 2021**[51] Williams, K. et al. Symptoms and impact of aromatic L-amino acid decarboxylase (AADC) deficiency: a qualitative study and the development of a patient-centred conceptual model. Curr Med Res Opin 37, 1353–1361 (2021) **Williams 2022**[11] Williams, Skrobanski, Buesch, Acaster 2022. Symptoms and impacts of aromatic L-amino acid decarboxylase (AADC) deficiency among individuals	**Williams 2021**[170] Williams, K. et al. SYMPTOMS AND IMPACT OF AROMATIC L-AMINO ACI DECARBOXYLASE DEFICIENCY (AADCD): A QUALITATIVE STUDY. Value in Health (2021).

		with different levels of motor function. Orphanet J Rare Dis . 2022 Mar 21;17(1):128. doi: 10.1186/s13023-022-02274-0.	
	Caregiver QoL	**Skrobanski 2021**[12] Skrobanski, H. et al. The impact of caring for an individual with aromatic L-amino acid decarboxylase (AADC) deficiency: a qualitative study and the development of a conceptual model. Current Medical Research and Opinion 37, 1821–1828 (2021).	**Skrobanski 2021**[61] Skrobanski et al., A qualitative study on the impact of caring for an individual with aromatic L-amino acid decarboxylase deficiency (AADCd). https://www.ispor.org/heor-resources/presentations-database/presentation/intl2021-3340/110561 (2021)
Cost and resource use	**Caregiver survey**	None	**Buesch 2022**[171] Buesch, K., Williams, K., Skrobanski, H. & Acaster, S. POSA359 Caring for an Individual with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Results from a Caregiver Questionnaire. Value Health 25, S219 (2022). **Buesch 2021**[171] Buesch, K., Willams, K. & Skrobanski, H. Caring for an Individual with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Results from a Caregiver Questionnaire. Value in Health (2021).
	Clinician survey	None	Two abstracts reporting the same clinician-led survey. **Saberian 2021**[112] Saberian, S., Rowan, P. & Patel, P. et al. Disease Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Healthcare Resource Use (HCRU) Overall and by Disease Severity. Value in Health (2021)

Abbreviations: DCE – Discrete choice experiment; HRQoL – Health-related quality-of-life; QoL – Quality-of-life

Appendix I: Cost and healthcare resource identification, measurement, and valuation

I1.1 Search strategy

For the SLR, the following databases were searched: Embase (covers biomedical literature from 1974 to present), MEDLINE (covers journals from 1966 to present), Embase Classic (the Embase back file covering citations between 1947 and 1973).

Supplementary searches of “grey” literature were performed using set search terms in Google Scholar, NICE website, Pharmaceutical Benefits Advisory Committee (PBAC) website, Canadian Agency for Drugs and Technologies in Health (CADTH) website, Scottish Medicines Consortium (SMC) website and Institute for Clinical and Economic Review (ICER) website.

Furthermore, searches included clinicaltrials.gov, the manufacturer’s repository of evidence, websites of manufacturers of comparator products, and bibliographic searching of any SLRs identified during screening. The following relevant congresses were also searched with a date restriction, where possible, over the last three years (2019–2022): The Professional Society for Health Economics and Outcomes Research (ISPOR) conference proceedings (EU), ISPOR conference proceedings (US), European Paediatric Neurology Society, Society for the Study of Inborn Errors of Metabolism, International Congress of Inborn Errors of Metabolism, British Paediatric Neurology Association., World Orphan Drug Congress, European Society for Gene and Cell Therapy, American Society of Gene and Cell Therapy, Gene Therapy for Neurological Disorders (US/EU).

Table 123: Embase, MEDLINE and Embase Classic (Embase index terms used as all databases were searched within the Embase interface) [date searched: 23rd February 2022]

Description	Search terms	Hits
Population	'aromatic amino acid decarboxylase deficiency'/exp OR 'aadc gene' OR 'AADC-deficiency' OR 'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR 'aadc-d' OR 'dopa decarboxylase deficiency' OR 'ddc gene' OR 'ddc deficiency' OR ‘aadc-d’ OR ‘aadc varian*’ OR ‘aadc syndrom*’ OR ‘aadc disease’ OR ‘aadc disorder’	551
Interventions/ comparators	‘Upstaza’ OR ‘AAV2 NEAR/2 hAADC’ OR ‘adeno-associated virus adj8 human AADC’ OR ‘eladocagene exuparvovec’ OR ‘AGIL NEAR/2 AADC’	50

Description	Search terms	Hits
Study types: RCT Filter	('clinical trial'/de OR 'randomised controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomisation'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	2,480,623
Observation study filter	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomised controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow-up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross-sectional' NEXT/1 (study OR studies)):ti,ab)	3,941,832
Combine filters and restrict date	#1 OR #2 AND (#3 OR #4) AND [humans]/lim	113
Economic Filter	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,037,062
Quality-of-life filter[134] (https://abstracts.cochrane.org/2015-vienna/ sensitivity-search-filter-designed-identify-studies-reporting-health-state-utility)	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR (caregiver OR carer)	1,194,398
Resource use filter	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti	2,041,276

Description	Search terms	Hits
	OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti) OR (carer OR carers OR caregiver OR caregivers)	
Combine terms and restrict date	#1 AND (#6 OR #7 OR #8) AND [humans]/lim	35
Combine terms	#5 OR #9	142

Abbreviations: RCT – Randomized control trial

Table 124: CENTRAL and Cochrane Clinical Answers (Cochrane Library interface) [date searched: 23rd February 2022]

Clinical search strategy		
Description	**Search terms**	**Hits**
Terms for population	"aromatic amino acid decarboxylase deficiency" OR "aadc gene" OR "AADC-deficiency" OR "aromatic amino acid decarboxylase deficiency" OR "aromatic L-amino acid decarboxylase deficiency" OR "aadc-d" OR "dopa decarboxylase deficiency" OR "ddc gene" OR "ddc deficiency" OR "aadc-d"	2
MeSH terms for population	MeSH descriptor [aromatic L-amino acid decarboxylase] explode all trees	11
Interventions/comparators	“Upstaza®” OR “AAV2” NEAR/2 “hAADC” OR “adeno-associated virus” adj8 “human AADC” OR “eladocagene exuparvovec” OR “AGIL” NEAR/2 “AADC”	0
Combine terms	#1 OR #2 OR #3 in trials	12

Abbreviations: MeSH – Medical subject heading

Table 125: ScHARRHUD search strategy [date searched: 23rd February 2022]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc-d’ OR ‘AADC-deficiency’	0

Abbreviations: HRQoL – Health-related quality-of-life; ScHARRHUD - School of health and related research, University of Sheffield

Table 126: EuroQoL database search strategy [date searched: 23rd February 2022]

HRQoL search strategy		
Description	**Search terms**	**Hits**
Terms for population	'aromatic amino acid decarboxylase deficiency' OR 'aromatic L-amino acid decarboxylase deficiency' OR ‘aadc-d’ OR ‘aadc-d’ OR ‘AADC-deficiency’	0

Abbreviations: HRQoL – Health-related quality-of-life

Table 127: NHS HTA and EED search strategy (via University of York website) [date searched: 23rd February 2022]

CRD HTA and EED database - Cost-effectiveness, cost and resource use and quality-of-life search strategy		
Description	**Search terms**	**Hits**
Terms for population	aromatic amino acid decarboxylase deficiency OR aromatic L-amino acid decarboxylase deficiency OR aadc-d OR aadc-d OR AADC-deficiency	0
Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	25,686
Combine filters	#1 AND #2 in NHSEED, HTA	0
QoL filter	qol OR quality-of-life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	13,073
Combine terms	#1 AND #4 in NHSEED, HTA	0

Abbreviations: CRD – Centre for reviews and dissemination; EED – Economic evaluation database; HTA – Health technology assessment; NHS – National health service; QoL – Quality-of-life

I1.2 Study selection

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified publications based on title and abstract (first pass) for inclusion using the review question and selection criteria. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in line with NICE guidelines.

Following the completion of first pass, full text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria by two independent reviewers. A discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required, in alignment with NICE guidance.

I1.3 Data extraction

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers or by consulting a third reviewer if necessary. For each publication, data were extracted into a data collection form (Excel based with tables suitably formatted to align with NICE 2022 SLR template) and developed in line with the University of York CRD and NICE reporting requirements.[135,136] A quality assessment of cost-effectiveness publications was conducted using the Drummond and Jefferson criteria[137].

I1.4 Selection criteria

Table 128: Selection criteria for Review Question 4 (cost and resource use studies)

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with AADC deficiency Carers/caregivers of patients with AADC deficiency	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	No restriction on intervention/comparator	No intervention / comparators of interest
Outcomes	Unit costs Resource use Budget impact Cost of illness	No reported outcomes of interest
Study type	Cost study Burden of disease study Resource use study Economic evaluations: o Cost-effectiveness analysis o Cost-utility analysis o Cost-benefit analysis o Cost-minimisation analysis o WTP studies o EEACT	Individual case study reports
Publication type	Article, conference abstract, conference paper, article in press	Short survey Reviews Letters Comment articles
Language	English	Non-English

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; EEACT – Economic evaluation alongside clinical trials; QALY – Quality-adjusted life-year; SLR – Systematic literature review; WTP – Willingness to pay

Please refer to Appendix D: Identification, selection and synthesis of clinical evidence for all publications excluded at the first and second pass stages, with reasons for justification provided for those excluded at the second pass stage. Please see Table 129 for a summary of the cost and resource use publications identified as part of the SLR.

Table 129: Summary of cost and resource use publications (n=14)

Reference	Year	Country	Patient population	Costs	Resource use
Buesch *et al.,* 2021(a)[13] *Caring for an individual with aromatic L-amino acid decarboxylase (aadc) deficiency: analysis of reported time for practical and emotional care and paid/unpaid help*	NR	NR	Questionnaires were completed by primary caregivers of individuals with AADC deficiency who had consented to take part in a qualitative interview. Twelve caregivers completed the questionnaire (10 parents, 1 brother, 1 aunt; mean age 44 years)	NR	- Participants reported seeing a mean of 8 (1-24) clinicians/experts before diagnosis. Mean time from first symptom to seeking medical care was 2.5 months, and from seeking medical care to final diagnosis 16.5 months (total mean 19 months). - Caregivers spent an average of 90 hours (56-140h) per week on practical and emotional care for their child, plus a mean of 15 hours (7-33h) per week on administrative tasks such planning activities or travelling to/attending appointments related to their child AADC deficiency. - 55% received paid and/or unpaid help with care. Unpaid support was provided mainly by the partner (mean 37 hours (8-93 h) per week); while paid support was provided by a registered nurse or training nursing assistant (mean 27 hours (10-35 h) per week). The latter was paid out of pocket or provided by the national service. - 75% of caregivers reported that they stopped working or reduced their working hours.
Buesch *et al.*, 2021(b)[172] *Economic Burden of Informal Care and Productivity Loss Due to Caring for Individuals with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: An Analysis for the US*	NR	USA	Patients with AADC deficiency	- Annual informal care = $5.4 million - Annual family income loss = $466,000"	- Seven US caregivers completed the questionnaire and reported an average of 111 (range: 84-147) hours/week spent on practical and emotional care for their child - A mean of 16 (range: 12-22) hours/week on administrative tasks and travelling/attending medical appointments. - 14% (1/7) received unpaid support provided by the partner (12 hours/week) - 43% (3/7) of caregivers had stopped working - With expected 30 new patients and their families in the country, the total number of hours needed for informal care was 200,741 annually, which corresponds to $5.4 million for informal care - Hours of loss of productivity were estimated to be 17,206 annually, leading to an estimated $466,000 of family income loss.
Buesch *et al.*, 2021(c)[171] *Caring for an Individual with Aromatic L-amino Acid*	NR	NR	Patients with AADC deficiency	NR	- The primary caregiver reported spending an average of 109 hours (range: 66h-166h) per week on care including practical, emotional care and administrative tasks such as scheduling and attending physician appointments

Decarboxylase (AADC) Deficiency: Results from a Caregiver Questionnaire					- 50% (N=7/14) of caregivers received unpaid support, which was mainly provided by their partner (mean 37 hours; range: 8h-93h per week) - 23% (N=3/13) received paid support from a nurse or trained nursing assistant (mean 27 hours; range: 10h-35h per week) - Overall, 43% (N=6/14) of the primary caregivers reported that they stopped working and 29% (N=4/14) reported having reduced their working hours, including both of the two parents of the same individual - An additional 14% (N=2/14) reported that their partners also reduced their working hours.
Fernández-Cortés *et al.* 2021[173] *Healthcare Resource Consumption Associated with Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D) in Italy*	NR	Italy	Data was reported on 11 patients (7 able to walk unassisted: group A-, 2 able to sit unassisted: group B-, and 2 with no motor function/head control only: group C-)	NR	- All patients were followed by neurologists, but only 73% by general practitioners or other specialists (paediatricians 45%; gastroenterologists 36%) - Psychiatrist visits were reported for patients of groups A and C (71%/100%), and pulmonologist and endocrinologist for group B (50%). - All groups required physiotherapy (64%). Other paramedical support varied: neuro-psychomotor therapy (55%, except patients of group B), occupational therapy (100% of group C), and nurses, speech therapists and dietitians (only group A). - Drug treatments included vitamin B6 (82%) and L-dopa (27%) for all, dopamine agonists (86%/100%) and MAO inhibitors (71%/50%) in patients of group A and C respectively, and sleep/mood disorders drugs (50%) in group B. - Surgeries were reported only for patients in group A. Medical devices (including verticalizers, and wheelchairs) were only reported in groups B and C. - Prolactin (91%), blood (82%), urine (82%) and iron level (73%) tests and ECG (82%), were common to all groups; groups A and B had a wider mix of medical procedures. - Overall, 73% of patients had 2.25 (±0.71) hospitalizations (>1 night) per year
Saberian *et al.*, 2021[112] *Disease Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Healthcare Resource Use (HCRU) Overall and by Disease Severity*	NR	France, Italy, and Spain	11 clinicians involved in the management of patients with AADC deficiency participated in the interviews (6 from	NR	- Eleven clinicians involved in the management of patients with AADC deficiency participated in the interviews (6 from France, 4 from Italy and 1 from Spain) providing information on 20 patients (10 were able to stand/walk with assistance, 2 were able to sit, and 8 had no motor function/head control) - Paramedical support was mainly provided by physiotherapists (75% of all patients [60% in patients able to

			France, 4 from Italy and 1 from Spain) providing information on 20 patients		stand/walk with assistance, 50% in patients able to sit, and 100% in patient with no motor function/head control]) - All recommended medications were used. Medical device use was higher in patients with no motor function/head control (i.e. 75% needed a manual and/or electric wheelchair). - Hospitalizations were frequent with a mean (SD) number of hospitalisations since diagnosis of 19.66 (46.03) due to uncontrollable movements."
Lee *et al.*, 2018[153] *Gene Therapy for AADC Deficiency Results in De Novo Dopamine Production and Supports Durable Improvement in Major Motor Milestones*	NR	National Taiwan University Children Hospital	25 children with AADC deficiency using a single administration of AGIL-AADC delivered bilaterally to the putamen by stereotactic infusions during a single, operative session in singlearm, open label clinical studies	NR	Regarding ambulatory function: - Two patients are using wheeled walkers - One additional patient is able to take steps holding an examiner's hand - One patient is walking independently
Buesch *et al.,* 2022[171] *POSA359 Caring for an Individual with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Results from a Caregiver Questionnaire*	NR	NR	NR	NR	- The primary caregiver reported spending an average of109 hours per week on care (practical care, emotional care and administrative tasks). - 50% of caregivers received unpaid support. - Overall, 43% of the primary caregivers reported that they stopped working and 29% reported reducing their hours. - Caregivers spend almost every waking moment caring for the individual with AADC.
Fernandez-Cortes *et al.,* 2022[173] *POSC69 Healthcare Resource Consumption Associated with Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D) in Italy*	NR	Italy	Patients with AADC deficiency	NR	- All groups required physiotherapy (64%). - Other paramedical support varied: neuro-psychomotor therapy (55%, except patients of group B), occupational therapy (100% of group C), and nurses, speech therapists and dietitians (only group A). - Drug treatments included vitamin B6 (82%) and L-dopa (27%) for all, dopamine agonists (86%/100%) and MAO inhibitors (71%/50%) in patients of group A and C respectively, and sleep/mood disorders drugs (50%) in group B. - Surgeries were reported only for patients in group A. - Medical devices (including verticalizers, and wheelchairs) were only reported in groups B and C.

					- Prolactin (91%), blood (82%), urine (82%) and iron level (73%) tests and ECG (82%), were common to all groups; groups A and B had a wider mix of medical procedures. - Overall, 73% of patients had 2.25 (±0.71) hospitalizations (>1 night) per year
Simons *et al.,* 2022[88] *POSC107 Long Term Outcomes for Patients with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: A Modelling Study Exploring the Benefit of Gene Therapy*			Patients with AADC deficiency	Cost benefits were found for medication and resource usage.	Cost benefits were found for medication and resource usage.
Solanke *et al.,* 2022[174] *POSA360 Economic Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency in Europe, from the Caregivers Perspective*	NR	Belgium, Italy, Spain and UK	Caregiver perspective	- Annually, 9,360 - 74,880 hours on average were spent on practical and emotional care, representing an estimated total of €111,852 to €1.6 million. - Caregivers further spent 30 to 240 hours weekly on average (1,560 – 12,480 hours/year) on administrative tasks, representing an estimated total of €358 – €5,112 per week (€18,642 – 265,824 annually). - 55% of caregivers received 35 to 277 hours weekly in paid and unpaid support (1,798 - 14,380 hours/ year), translating into an estimated total of €493 - €5,866 weekly (€25,625 to €305,006 annually). - For countries studied, the resulting total cost of caregiving ranged from €5,206 - €24,018 weekly (€156,119 to €2.2 million per annum). - Further, the loss of income owing to 75% of primary caregivers leaving work or reducing working hours was estimated to €16,658 - €227,429 per year	
Bergkvist *et al.,* 2021[8] *Aromatic L-amino acid decarboxylase deficiency – a systematic review*	NR	NR	Patients with AADC deficiency	NR	Drugs commonly reported for treating AADC include pyridoxine/B6
Boehnke *et al.,* 2021(a)[158] *Gene Therapy for Rare Diseases: Differences to Chronic Therapy and the Example of AADC Deficiency*	NR	NR	Patients with AADC deficiency	For gene therapies for rare diseases (as per the AIM definition, with a prevalence of less than 1:100,000) an estimated € 370,000 is expected for each patient.	The treatment is given during a single surgical session, and this lasts for many hours
Boehnke *et al.,* 2021(b)[175] *POSC384 Aromatic L-amino Acid Decarboxylase (AADC)*	NR	NR	Patients with AADC deficiency	NR	- All described patients (100%) had a neurologist involved in their management. - Other specialists reported being involved in their care were paediatricians (67%), dieticians (67%), gastroenterologists

Deficiency in UK: Burden of Disease					(50%), physiotherapists (50%), speech therapists (50%), cardiologists (50%), (community) psychiatrists (33%), endocrinologists (17%), orthopaedic physicians (17%), and respiratory specialists (17%). - Patients used a wide range of treatments (4-14 medications to treat AADC deficiency symptoms) usually initiated at time of symptoms' onset.

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; HCRU – Healthcare resource use; NR – Not reported; SD – Standard deviation; USA – United States of America

Table 130: Summary of cost and resource use publications (n=14)

Reference	Year	Country	Patient population	Costs	Resource use
Buesch *et al.,* 2021(a)[13] *Caring for an individual with aromatic L-amino acid decarboxylase (aadc) deficiency: analysis of reported time for practical and emotional care and paid/unpaid help*	NR	NR	Questionnaires were completed by primary caregivers of individuals with AADC deficiency who had consented to take part in a qualitative interview. Twelve caregivers completed the questionnaire (10 parents, 1 brother, 1 aunt; mean age 44 years)	NR	- Participants reported seeing a mean of 8 (1-24) clinicians/experts before diagnosis. Mean time from first symptom to seeking medical care was 2.5 months, and from seeking medical care to final diagnosis 16.5 months (total mean 19 months). - Caregivers spent an average of 90 hours (56-140h) per week on practical and emotional care for their child, plus a mean of 15 hours (7-33h) per week on administrative tasks such planning activities or travelling to/attending appointments related to their child AADC deficiency. - 55% received paid and/or unpaid help with care. Unpaid support was provided mainly by the partner (mean 37 hours (8-93 h) per week); while paid support was provided by a registered nurse or training nursing assistant (mean 27 hours (10-35 h) per week). The latter was paid out of pocket or provided by the national service. - 75% of caregivers reported that they stopped working or reduced their working hours.
Buesch *et al.*, 2021(b)[172] *Economic Burden of Informal Care and Productivity Loss Due to Caring for Individuals with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: An Analysis for the US*	NR	USA	Patients with AADC deficiency	- Annual informal care = $5.4 million - Annual family income loss = $466,000"	- Seven US caregivers completed the questionnaire and reported an average of 111 (range: 84-147) hours/week spent on practical and emotional care for their child - A mean of 16 (range: 12-22) hours/week on administrative tasks and travelling/attending medical appointments. - 14% (1/7) received unpaid support provided by the partner (12 hours/week) - 43% (3/7) of caregivers had stopped working

					- With expected 30 new patients and their families in the country, the total number of hours needed for informal care was 200,741 annually, which corresponds to $5.4 million for informal care - Hours of loss of productivity were estimated to be 17,206 annually, leading to an estimated $466,000 of family income loss.
Buesch *et al.*, 2021(c)[171] *Caring for an Individual with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Results from a Caregiver Questionnaire*	NR	NR	Patients with AADC deficiency	NR	- The primary caregiver reported spending an average of 109 hours (range: 66h-166h) per week on care including practical, emotional care and administrative tasks such as scheduling and attending physician appointments - 50% (N=7/14) of caregivers received unpaid support, which was mainly provided by their partner (mean 37 hours; range: 8h-93h per week) - 23% (N=3/13) received paid support from a nurse or trained nursing assistant (mean 27 hours; range: 10h-35h per week) - Overall, 43% (N=6/14) of the primary caregivers reported that they stopped working and 29% (N=4/14) reported having reduced their working hours, including both of the two parents of the same individual - An additional 14% (N=2/14) reported that their partners also reduced their working hours.
Fernández-Cortés *et al.* 2021[173] *Healthcare Resource Consumption Associated with Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D) in Italy*	NR	Italy	Data was reported on 11 patients (7 able to walk unassisted: group A-, 2 able to sit unassisted: group B-, and 2 with no motor function/head control only: group C-)	NR	- All patients were followed by neurologists, but only 73% by general practitioners or other specialists (paediatricians 45%; gastroenterologists 36%) - Psychiatrist visits were reported for patients of groups A and C (71%/100%), and pulmonologist and endocrinologist for group B (50%). - All groups required physiotherapy (64%). Other paramedical support varied: neuro-psychomotor therapy (55%, except patients of group B), occupational therapy (100% of group C), and nurses, speech therapists and dietitians (only group A). - Drug treatments included vitamin B6 (82%) and L-dopa (27%) for all, dopamine agonists (86%/100%) and MAO inhibitors (71%/50%) in patients of group A and C respectively, and sleep/mood disorders drugs (50%) in group B. - Surgeries were reported only for patients in group A. Medical devices (including verticalizers, and wheelchairs) were only reported in groups B and C.

					- Prolactin (91%), blood (82%), urine (82%) and iron level (73%) tests and ECG (82%), were common to all groups; groups A and B had a wider mix of medical procedures. - Overall, 73% of patients had 2.25 (±0.71) hospitalizations (>1 night) per year
Saberian *et al.*, 2021[112] *Disease Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Healthcare Resource Use (HCRU) Overall and by Disease Severity*	NR	France, Italy, and Spain	11 clinicians involved in the management of patients with AADC-d participated in the interviews (6 from France, 4 from Italy and 1 from Spain) providing information on 20 patients	NR	- Eleven clinicians involved in the management of patients with AADC deficiency participated in the interviews (6 from France, 4 from Italy and 1 from Spain) providing information on 20 patients (10 were able to stand/walk with assistance, 2 were able to sit, and 8 had no motor function/head control) - Paramedical support was mainly provided by physiotherapists (75% of all patients [60% in patients able to stand/walk with assistance, 50% in patients able to sit, and 100% in patient with no motor function/head control]) - All recommended medications were used. Medical device use was higher in patients with no motor function/head control (i.e. 75% needed a manual and/or electric wheelchair). - Hospitalizations were frequent with a mean (SD) number of hospitalisations since diagnosis of 19.66 (46.03) due to uncontrollable movements."
Lee *et al.*, 2018[153] *Gene Therapy for AADC Deficiency Results in De Novo Dopamine Production and Supports Durable Improvement in Major Motor Milestones*	NR	National Taiwan University Children Hospital	25 children with AADC deficiency using a single administration of AGIL-AADC delivered bilaterally to the putamen by stereotactic infusions during a single, operative session in singlearm, open label clinical studies	NR	Regarding ambulatory function: - Two patients are using wheeled walkers - One additional patient is able to take steps holding an examiner's hand - One patient is walking independently
Buesch *et al.*, 2022[171] *POSA359 Caring for an Individual with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: Results from a Caregiver Questionnaire*	NR	NR	NR	NR	- The primary caregiver reported spending an average of109 hours per week on care (practical care, emotional care and administrative tasks). - 50% of caregivers received unpaid support. - Overall, 43% of the primary caregivers reported that they stopped working and 29% reported reducing their hours.

					- Caregivers spend almost every waking moment caring for the individual with AADC.
Fernandez-Cortes *et al.,* 2022[173] *POSC69 Healthcare Resource Consumption Associated with Aromatic L-amino Acid Decarboxylase Deficiency (AADC-D) in Italy*	NR	Italy	Patients with AADC deficiency	NR	- All groups required physiotherapy (64%). - Other paramedical support varied: neuro-psychomotor therapy (55%, except patients of group B), occupational therapy (100% of group C), and nurses, speech therapists and dietitians (only group A). - Drug treatments included vitamin B6 (82%) and L-dopa (27%) for all, dopamine agonists (86%/100%) and MAO inhibitors (71%/50%) in patients of group A and C respectively, and sleep/mood disorders drugs (50%) in group B. - Surgeries were reported only for patients in group A. - Medical devices (including verticalizers, and wheelchairs) were only reported in groups B and C. - Prolactin (91%), blood (82%), urine (82%) and iron level (73%) tests and ECG (82%), were common to all groups; groups A and B had a wider mix of medical procedures. - Overall, 73% of patients had 2.25 (±0.71) hospitalizations (>1 night) per year
Simons *et al.,* 2022[88] *POSC107 Long Term Outcomes for Patients with Aromatic L-amino Acid Decarboxylase (AADC) Deficiency: A Modelling Study Exploring the Benefit of Gene Therapy*			Patients with AADC deficiency	Cost benefits were found for medication and resource usage.	Cost benefits were found for medication and resource usage.
Solanke *et al.,* 2022[174] *POSA360 Economic Burden of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency in Europe, from the Caregivers Perspective*	NR	Belgium, Italy, Spain and UK	Caregiver perspective	- Annually, 9,360 - 74,880 hours on average were spent on practical and emotional care, representing an estimated total of €111,852 to €1.6 million. - Caregivers further spent 30 to 240 hours weekly on average (1,560 – 12,480 hours/year) on administrative tasks, representing an estimated total of €358 – €5,112 per week (€18,642 – 265,824 annually). - 55% of caregivers received 35 to 277 hours weekly in paid and unpaid support (1,798 - 14,380 hours/ year), translating into an estimated total of €493 - €5,866 weekly (€25,625 to €305,006 annually). - For countries studied, the resulting total cost of caregiving ranged from €5,206 - €24,018 weekly (€156,119 to €2.2 million per annum). - Further, the loss of income owing to 75% of primary caregivers leaving work or reducing working hours was estimated to €16,658 - €227,429 per year		

Bergkvist *et al.*, 2021[8] *Aromatic L-amino acid decarboxylase deficiency – a systematic review*	NR	NR	Patients with AADC deficiency	NR	Drugs commonly reported for treating AADC include pyridoxine/B6
Boehnke *et al.*, 2021(a)[158] *Gene Therapy for Rare Diseases: Differences to Chronic Therapy and the Example of AADC Deficiency*	NR	NR	Patients with AADC deficiency	For gene therapies for rare diseases (as per the AIM definition, with a prevalence of less than 1:100,000) an estimated € 370,000 is expected for each patient.	The treatment is given during a single surgical session, and this lasts for many hours
Boehnke *et al.*, 2021(b)[175] *POSC384 Aromatic L-amino Acid Decarboxylase (AADC) Deficiency in UK: Burden of Disease*	NR	NR	Patients with AADC deficiency	NR	- All described patients (100%) had a neurologist involved in their management. - Other specialists reported being involved in their care were paediatricians (67%), dieticians (67%), gastroenterologists (50%), physiotherapists (50%), speech therapists (50%), cardiologists (50%), (community) psychiatrists (33%), endocrinologists (17%), orthopaedic physicians (17%), and respiratory specialists (17%). - Patients used a wide range of treatments (4-14 medications to treat AADC deficiency symptoms) usually initiated at time of symptoms' onset.

Abbreviations: AADC-d – Aromatic L-amino acid decarboxylase deficiency; HCRU – Healthcare resource use; NR – Not reported; SD – Standard deviation; USA – United States of America

I1.5 Search results

Of the 166 publications identified across the SLR for title and abstract screening, 12 were considered for full text review of review question 4: cost and resource use publications.

Following review of the full texts, 5 publications were excluded because they did not meet the selection criteria: 4 did not meet the outcomes criteria, and 1 was unavailable. A grey literature search provided an additional 7 cost and resource use studies which met the inclusion criteria. Overall, 14 publications met the selection criteria following the first and second pass of the cost and resource use studies review and were extracted.

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

J.1.1 Using individual patient PDMS-2 trajectories to model efficacy outcomes

The CEA uses individual patient PDMS-2 trajectories to determine motor milestone achievement, rather than using the average PDMS-2 trajectory from the 28 patients treated with eladocagene exuparvovec. Using individual trajectories is more appropriate because of the small sample size and high heterogeneity in PDMS-2 trajectories (as shown in Figure 58).

Figure 58 Relationship between total raw PDMS-2 score and age of patient treatment with eladocagene exuparvovec (n=28)

Abbreviations: PDMS-2 Peabody Development Motor Scale-2.
The different colours represent different patients. Patients had varying follow-up durations ranging from 18 months to 108 months.

J.1.2 Global symptom improvement in clinical trials for eladocagene exuparvovec

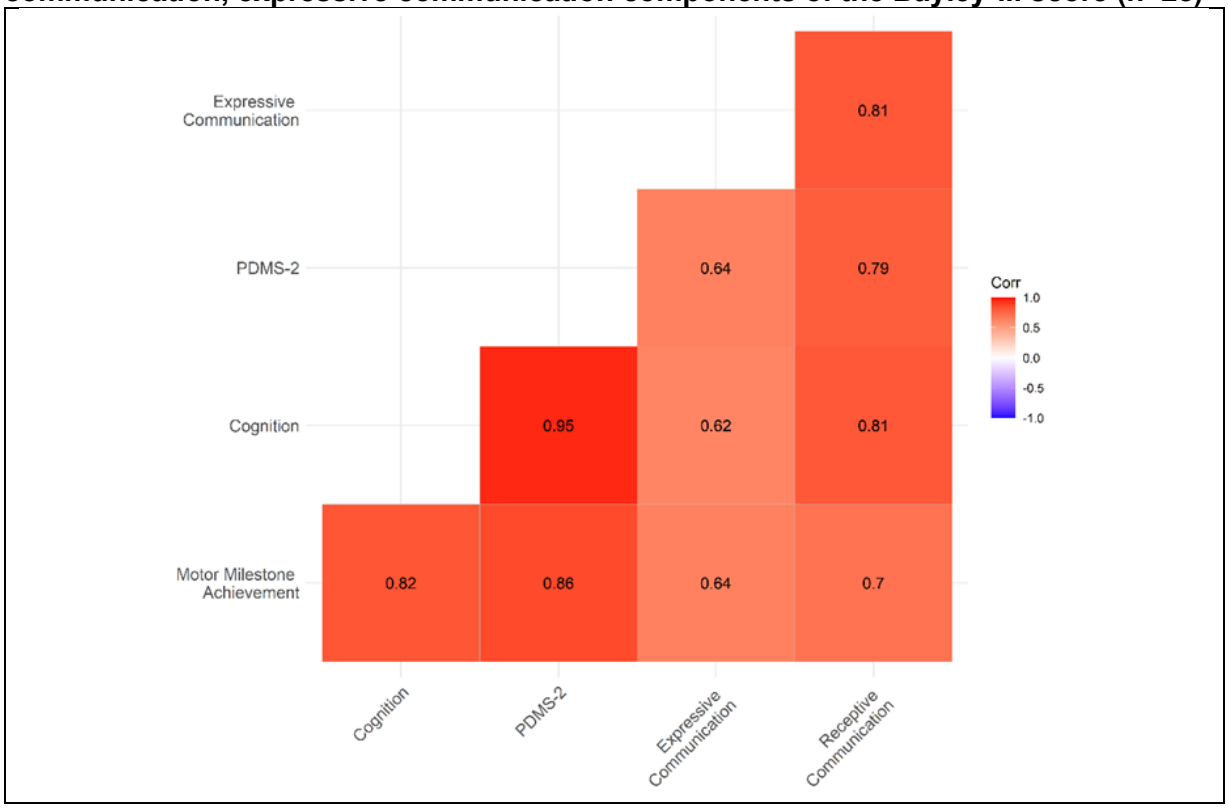
A key assumption in the CEA is that other symptoms of AADC deficiency improve as motor milestones improve in patients with AADC deficiency. This assumption is needed, in part, due to the challenges of accurately and robustly modelling multiple outcomes using such a small sample size.

To explore the validity of the assumption, the relationship between clinical outcomes in trials for eladocagene exuparvovec was explored. Figure 59, which presents the correlation coefficients of key clinical outcomes from the eladocagene exuparvovec clinical trials (n=28), shows a strong correlation between each outcome, including:

- **PDMS-2 strongly correlate with motor milestone achievement** (correlation coefficient of 0.86). This indicates that patients with higher PDMS-2 scores achieve higher motor milestones.
- **Bayley-III cognition and communication components strongly correlate with motor milestone achievement** (correlation coefficient of 0.82 for cognition and 0.64 and 0.70 for expressive and receptive communication, respectively). This shows that that patients with higher motor milestone attainment are more likely to have higher level of cognition and communication (further demonstrated in Figure 60 and Figure 61).
- **PDMS-2 scores strongly correlate with Bayley-III cognition and communication** (correlation coefficient of 0.95 for cognition and 0.64 and 0.79 for expressive and receptive communication, respectively). This shows that patients with higher motor development are more likely to have a higher level of cognition and communication.

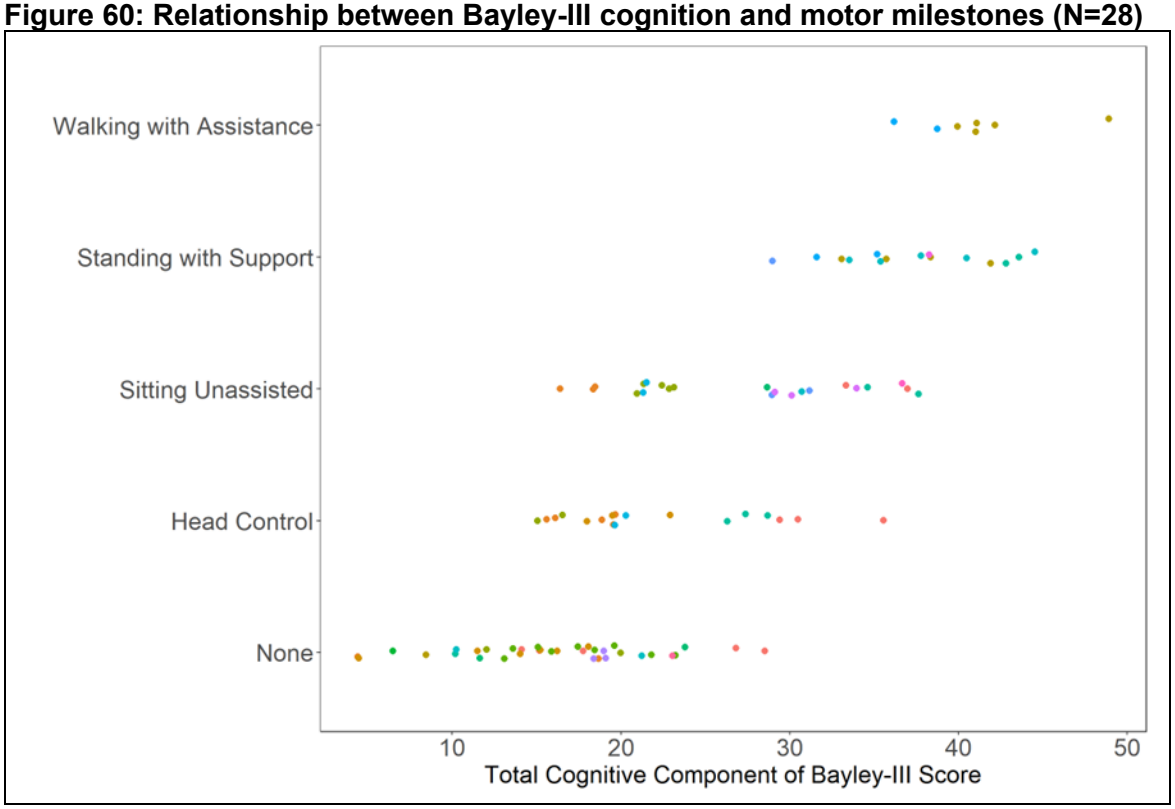
Based on the relationships described above, it was possible to conclude that PDMS-2 improvements would mean improvements in motor milestone achievement, cognition, and communication. Based on the above and the AADC deficiency literature[59], it was therefore concluded that a global symptom improvement assumption was appropriate (i.e. as motor function improves, other symptoms improve [OGC, dystonia, behaviour, feeding abnormalities etc]).

Figure 59: Correlation between motor milestones, PDMS-2, and cognition, receptive communication, expressive communication components of the Bayley-III score (n=28)



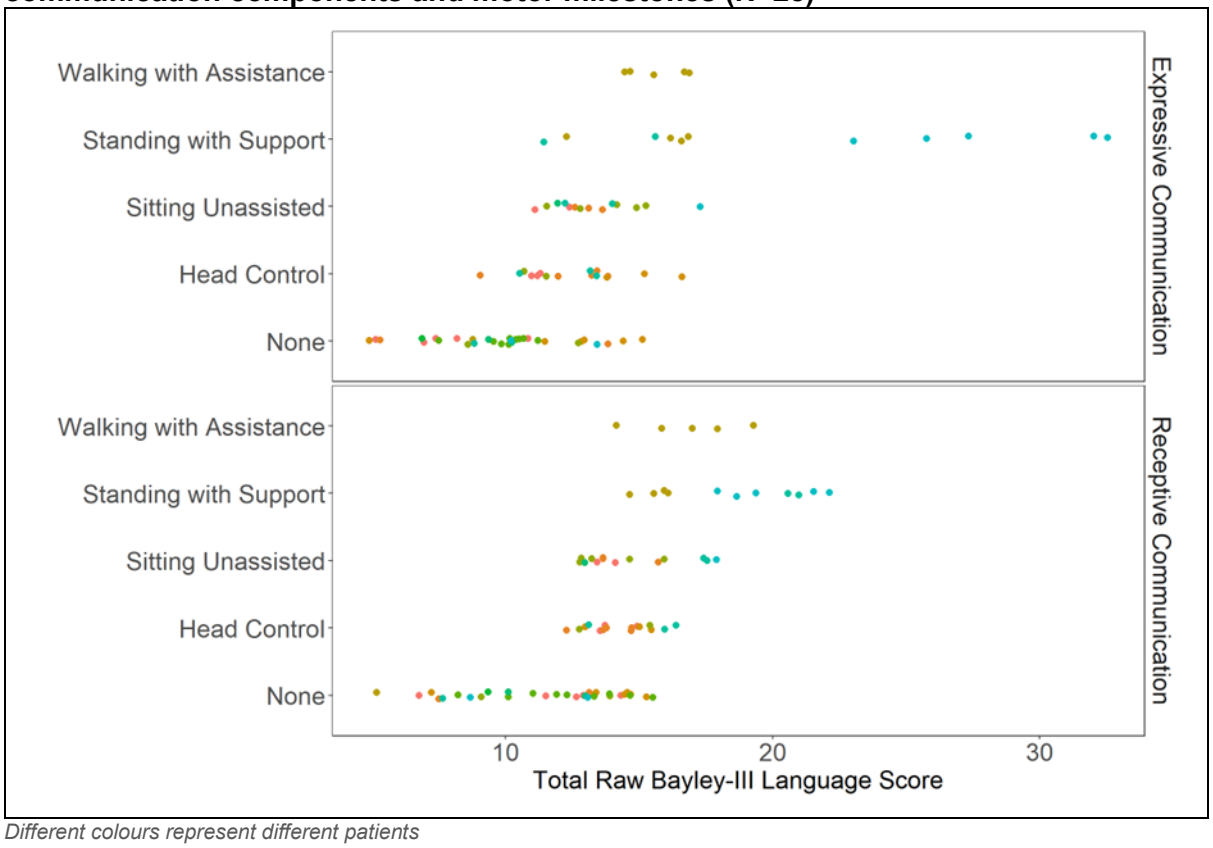
Abbreviations: PDMS-2 Peabody Development Motor Scale-2.

Figure 60: Relationship between Bayley-III cognition and motor milestones (N=28)



Different colours represent different patients

Figure 61: Relationship between Bayley-III expressive communication and receptive communication components and motor milestones (N=28)



Different colours represent different patients

J.1.3 Motor milestone prediction methodology

The CEA uses individual patient PDMS-2 scores to predict motor milestone achievement in a two-step process: Firstly, to account for missing and/or limited follow-up data for some patients, a Bayesian growth model was used to fit curves to the observed PDMS-2 trial data and observed data for the Bayley-III cognitive, expressive communication, and receptive communication scores. Secondly, the predicted PDMS-2 scores were used to predict motor milestone achievement using a cumulative ordered logit model.

The subsections below outline the process for determining the final models to predict motor milestone outcomes. Given the correlation between PDMS-2 scores and Bayley-III component scores, initial approaches considered the use of both of these outcomes to predict motor milestone achievement.

J.1.3.1 Overview

Motor milestone achievement in the economic model was predicted using two steps. Firstly, to account for missing and/or limited follow-up data for some patients, a Bayesian growth model was used to fit curves to the observed PDMS-2 and Bayley-III component scores. Secondly, the predicted scores were used to predict motor milestone achievement using a cumulative ordered logit model.

- **Step 1: Bayesian modelling to predict PDMS-2 and Bayley-III component scores:** Curves were fitted to observed individual patient PDMS-2 scores and Bayley-III cognitive, expressive communication and receptive communication component scores using a Bayesian growth model. The heterogeneity across patients in improvements in PDMS-2 and Bayley-III component scores indicates a mixed-effects model was appropriate. Bayesian regression models approaching an asymptote were fitted – namely asymptotic, logistic and Gompertz models. These models include mixed-effects that allow for different patients to have different trajectories for their scores. The use of fixed effects was considered for the growth models, however, due to the large degree of heterogeneity between the patients it was decided that a mixed-effects model was more appropriate. The optimal model was chosen based on goodness of fit statistics and after discussion with clinical experts on the validity of the predictions and their extrapolations.
- **Step 2: Cumulative ordered logit modelling to predict motor milestones:** The second stage of the model uses the predicted PDMS-2 and Bayley-III component scores from Step 1 to predict motor milestone achievement, using a cumulative ordered logit model, a type of cumulative ordered link model. The cumulative ordered link model was used for observations that fall into a finite ordered set of categories,[176] such motor milestones. The optimal model was chosen based on goodness of fit statistics and after discussion with clinical experts on the validity of the predictions and their extrapolations.

J.1.3.2 Rationale for Bayesian model

The mixed-effects models implemented in this Appendix all took a Bayesian approach. In a classical approach, a point estimate is produced with an associated 95% CI, whereas in a Bayesian approach, prior beliefs about the pooled effect is combined with the information from the patients to obtain the posterior distribution of the pooled effect from the patients.

The advantages of the Bayesian approach include being able to easily present inferences that fully consider uncertainty about all unknown quantities, including the extent of between patient heterogeneity. Unlike a microsimulation approach, the Bayesian approach does not add unnecessary computational burden in the modelling of outcomes. Additionally, the posterior probabilities estimated from a Bayesian analysis are often easier to interpret than the p-values from a classical approach.

In a mixed-effects model, both fixed and random effects are considered. Under a fixed effect, each patient is used to estimate an effect that is assumed to be common between patients, with any difference between the data from each patient is assumed to be due to sampling error. Under a random effects model, differences in the data between patients are assumed to be due to both sampling error and heterogeneity between patients. The small sample size and heterogeneity between patients means a random effects approach is more relevant. Preliminary analysis explored the use of fixed effects for the analysis, but led to poor goodness of fit and so the mixed effect approach was taken.

J.1.3.3 Bayesian model approach to predict PDMS-2 and Bayley-III component scores

For the Bayesian modelling to predict PDMS-2 and Bayley-III component scores, a series of models that approach an asymptote were fitted: namely asymptotic, Gompertz and logistic models. These were chosen as the clinical data indicate a plateauing of treatment benefit over time. The Michaelis-Menten model was also considered in preliminary work but was disregarded as it did not fit the data well and required for all patients to have a baseline test score of zero (not true for PDMS-2 and Bayley-III component scores). The approach to modelling was discussed and validated with HEOR experts in a series of advisory boards (March 2021).[53]

Each of the three model specifications took a different function form (Table 131) and while they all took a similar format, they each have different shape of model. Figure 62 presents an example schematic of each of these models. This is illustrated using hypothetical data that assumes a baseline score of 5; a maximum score of 100 (i.e., the asymptote is 100) and that at timepoint ten, patients will have reached score 99. In the logistic model (shown by the blue curve) the change in score over time takes an ‘S’ shape, with the rate of change being slow at first, then rising quickly before slowing down again reaching a final plateau. The Gompertz model (shown in the orange curve) also takes a similar ‘S’ shape but assumes a higher initial rate of increase in the score. In comparison, the asymptomatic model (shown by the grey curve) assumes that the largest rate of change in test scores appears at the start, with the rate slowing down earlier than in the logistic and Gompertz model before reaching the plateau.

Figure 62. Illustrative graph showing the differences between each of the three different growth model specifications

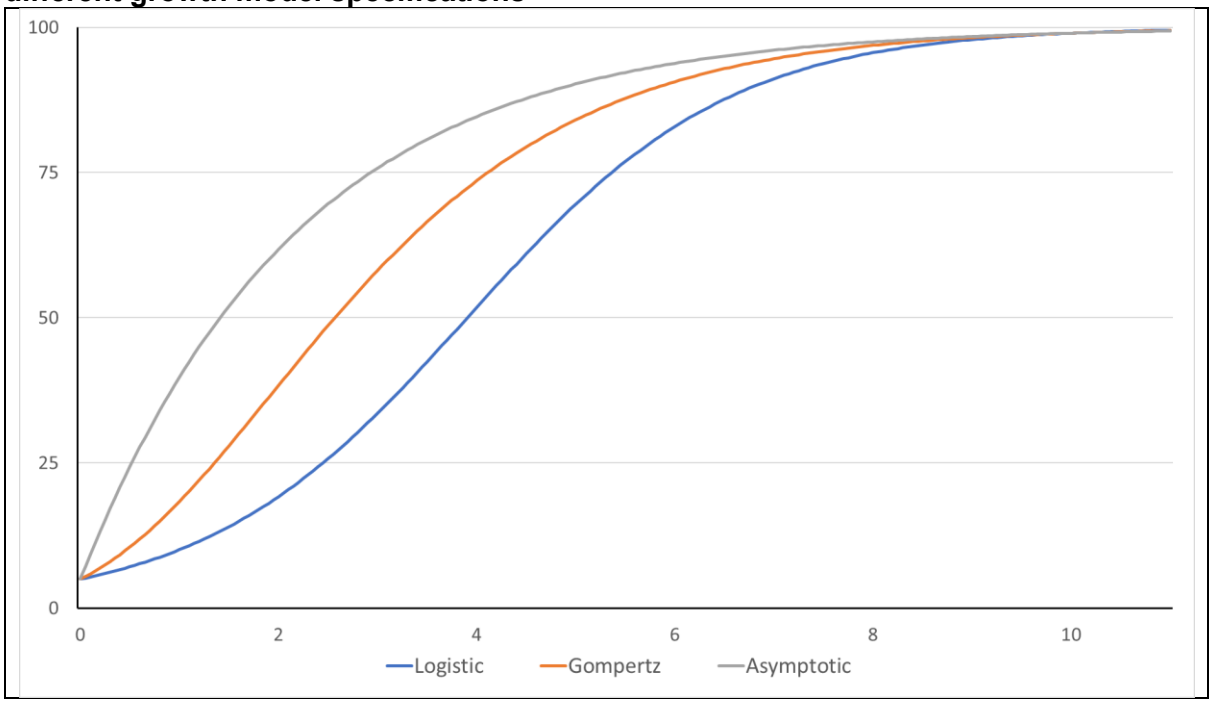


Table 131: Functional form of the model specifications

Growth Model	Functional Form
Logistic	$\frac{\alpha}{1 + exp\left(\frac{\beta - t}{\gamma}\right)}$
Gompertz	$\alpha \times exp(\beta \exp(\gamma \times t)$
Asymptotic	$\alpha + (\beta - \alpha) \times exp(-exp(\beta) \times t)$

The data suggests that age of a patient at baseline impacts on the progression of their test scores after treatment. Therefore, the parameters in each of the model functional forms $(\alpha_k, \beta_k, \gamma_k)$ have been assumed to take a linear form, such that, using α_k as an example:

$$\boldsymbol{\alpha_k = \alpha_0 + Age * \alpha_1}$$

Where, the parameters have an age independent component (α_0) and an age dependent component (α_1).

Due to the small amount of available data used to populate the models, situations where there is assumed to be no age independent variation in α (i.e., $\alpha_0 = 0$) and where α is assumed to be wholly independent of age (i.e., $\alpha_1 = 0$) were explored. In this analysis, the quantity of interest of the model is the score (i.e. the PDMS-2 and Bayley-III component score) of a patient k at time t. Let this be denoted x_{kt}. Then for each patient:

$$\boldsymbol{x_{kt} \sim N(\mu_{kt}, \sigma^2)}$$
$$\boldsymbol{\mu_{kt} = f(\Phi_k)}$$

$$\boldsymbol{\Phi}_{\{k)} = \{\boldsymbol{\alpha}_k, \boldsymbol{\beta}_k, \boldsymbol{\gamma}_k\}$$
$$\boldsymbol{\Phi}_{\mathbf{k}} \sim [.,.]$$

Where μ_{kt} is the mean score of patient k at time t. This is represented by a function $f(\boldsymbol{\Phi})$ defined by the chosen asymptotic model (see below). The parameters in $\boldsymbol{\Phi}$ represent the parameters in each of the model specifications (Table 131) and are assumed to be dependent on patient k and features age dependent and age independent components.

The functional form of $f(\boldsymbol{\Phi}_k)$ is presented for each of the three growth models fitted:

Case 1: Logistic Model

$$\boldsymbol{f(\Phi_k) = \frac{\alpha_k}{1 + exp\left(\frac{\beta_k - t}{\gamma_k}\right)}}$$

Under this specification α_k represents the maximum value patient k's score can reach over time in the model. $\frac{1}{\gamma_k}$ represents the modelled proportionate increase in the population in one time unit (here assumed to be one month) and $\exp\left(\frac{\beta_k}{\gamma_k}\right)$represents the patients modelled baseline score.

Case 2: Gompertz Model

$$\boldsymbol{f(\Phi_k) = \alpha_k\, exp\big(-\beta_k \backslash times\ exp\ (\gamma_k\ \backslash times\ t\big)}$$

Under this specification α_k represents the modelled asymptotic score for patient k; β_k represents the modelled displacement along the x-axis. That is β_k is used to dictate the patients modelled baseline score $(\alpha_k \exp(-\beta_k)))$ and γ_k dictates the rate of growth per unit of time.

Case 3: Asymptotic Model

$$\boldsymbol{f(\Phi_k) = \alpha_k + (\beta_k - \alpha_k)\, exp[-exp(\gamma_k)\, t]}$$

Under this specification, α_k represents the asymptote, i.e., the maximum score participant k can achieve under the model. β_k is the modelled baseline score for individual k and γ_k is the logarithm of the rate of change in test score per time period. Let A_k be the age of the patient at baseline when they receive eladocagene exuparvovec. Then, for all three cases:

$$\boldsymbol{\alpha_k = \alpha_k^{(1)} + A_k \alpha_k^{(2)}}$$
$$\boldsymbol{\beta_k = \beta_k^{(1)} + A_k \beta_k^{(2)}}$$
$$\boldsymbol{\gamma_k = \gamma_k^{(1)} + A_k \gamma_k^{(2)}}$$

The random effects distributions for the models are, for $k = \{1,2,\dots,K\}$:

$$\boldsymbol{\alpha_k^{(1)} \sim \log N(\alpha^{1a}, \sigma_{1a}^2)}$$
$$\boldsymbol{\alpha_k^{(2)} \sim \log N(\alpha^{2a}, \sigma_{2a}^2)}$$
$$\boldsymbol{\beta_k^{(1)} \sim N(\beta^{1b}, \sigma_{1b}^2)}$$
$$\boldsymbol{\beta_k^{(2)} \sim N(\beta^{2b}, \sigma_{12}^2)}$$
$$\boldsymbol{\gamma_k^{(1)} \sim N(\gamma^{1c}, \sigma_{1c}^2)}$$
$$\boldsymbol{\gamma_k^{(2)} \sim N(\gamma^{2c}, \sigma_{2c}^2)}$$

To fully specify the models, priors needed to be defined for the hyper-parameters and the covariate effects. Vague priors were used with their structure dependent on prior knowledge (i.e., restricted to the range of possible values, so parameters that represent standard deviations had prior distributions that are strictly positive).

$$\boldsymbol{\alpha^{1a}, \alpha^{2a}, \beta^{1a}, \beta^{2a}, \gamma^{1a}, \gamma^{2a} \sim N(0, 10^4)}$$
$$\boldsymbol{\sigma_{1a}, \sigma_{2a}, \sigma_{1b}, \sigma_{2b}, \sigma_{1c}, \sigma_{2c}, \sigma \sim U(0, 10^3)}$$

For each of the three model functional forms the following specifications were fitted in sequence:

- Assuming each parameter had a linear relationship with the age of the patient at baseline (**with** an age independent component – i.e., $\alpha_k^{(2)} \neq 0, \beta_k^{(2)} \neq 0, \gamma_k^{(2)} \neq 0$).
- Were any of $\alpha_k^{(2)}, \beta_k^{(2)}, \lambda\gamma_k^{(2)}$ in the above specification not significantly different to zero then it was assumed that they had no relationship with the age of the patient at baseline and they were removed from the model.
- The rate parameter (γ) does not depend on the patient (i.e., it is a fixed effect).
- The asymptote parameter (α) does not depend on the age of the patient at baseline.
- No parameters depend on the age of the patient at baseline.

Bayesian inference was performed by MCMC using JAGS software in R. Two chains were used with a burn-in period of 10,000 simulations with 100,000 simulations used in the analysis. Convergence was checked by inspection of the trace plots.

J.1.3.4 Cumulative ordered logit modelling to predict motor milestone attainment from predicted PDMS-2 and Bayley-III scores

As the meeting of motor milestones is a set of discrete ordered outcomes, a multinomial ordered logit model is used. This leverages the outcomes from the best fitting Bayesian growth models used to predict PDMS-2 and Bayley-III component scores. As with the prediction of PDMS-2 and Bayely-III component scores, a Bayesian approach was taken.

Let the 'observed' motor milestone be represented by a random variable Y_{kt} that takes a value of j if the t^{th} observation for the k^{th} patient lies in the j^{th} category, where j is the set of motor

milestones, namely: No motor function; full head control; sitting unassisted; standing with support; and walking with assistance.

The cumulative ordered link model took the following form:

$$\mathbf{T_{kt}} \sim \mathbf{Ordered\ Logit}(\boldsymbol{\mu_{kt}}, \boldsymbol{\theta})$$
$$\boldsymbol{\mu_{kt}} = \boldsymbol{\beta^T X}$$

Where μ_{kt} is the linear predictor estimated from the regression variables (X) including the PDMS-2 and Bayley-III scores in step one; $\boldsymbol{\beta}$ are the estimated parameters and $\boldsymbol{\theta} = \{\theta_j\}$ are the strictly ordered, estimated thresholds for the motor milestones.

$$\boldsymbol{\beta_i} \sim \boldsymbol{N(b_i, \sigma_1)}$$

Where *i* is the set of regression variables in the model in the specification for μ_{kt} (i.e., PDMS-2 score; Bayley-III component score, time since intervention).

Under the logistic model,

$$\mathbf{P}(\boldsymbol{Y_i > j |\ k, t}) = \frac{\boldsymbol{exp}(\boldsymbol{\mu_{kt} - \theta_j})}{\mathbf{1} + \boldsymbol{exp}\{\boldsymbol{\mu_{kt} - \theta_j}\}}$$

Where $\mathrm{P}(Y_i > j |\ k, t)$ is the probability that individual k is in a motor milestone category greater than j at time t. Therefore, $\mathrm{P}(Y_i = j | k, t)$ the probability that individual k is in motor milestone j at time t can be calculated by:

$$\mathbf{P}(\boldsymbol{Y_i = j}) = \mathbf{P}(\boldsymbol{Y_i \leq j}) - \mathbf{P}\big(\boldsymbol{Y_i \leq (j - 1)}\big)$$

To fully specify the models, priors needed to be defined for the hyper-parameters and the covariate effects. Vague priors were used with their structure dependent on prior knowledge (i.e., uniform distribution for strictly positive variables and normal distributions for variables that can take any value).

For each i:

$$\boldsymbol{b_i} \sim \boldsymbol{N}\big(\mathbf{0}, \mathbf{10^3}\big)$$
$$\boldsymbol{\sigma_i} \sim \boldsymbol{U}\big(\mathbf{0}, \mathbf{10^2}\big)$$

In addition:

$$\boldsymbol{\theta_j} \sim \boldsymbol{N}\big(\mathbf{0}, \mathbf{10^3}\big)$$

Where $\theta_j < \theta_{j+1}$ for j being the set of motor milestones.

The following model specifications were fitted:

Model fitted using observed values of PDMS-2 and the observed component Bayley scores:

$$X = \{PDMS_{kt}, Bayley_{ckt}\}$$

Where $PDMS_{kt}$ is the observed PDMS-2 score for patient k at time t; and $Bayley_{ckt}$ is the observed Bayley-III score for component c for patient k at time t

Two different model specifications were considered in this case. These were, just including the cognitive component of the Bayley-III and including the cognitive, expressive communication and receptive communication components of the Bayley-III.

Model fitted using observed values of PDMS-2:

$$X = \{PDMS_{kt}\}$$

Where $PDMS_{kt}$ is the observed PDMS-2 score for patient k at time t

Bayesian inference was performed by MCMC using JAGS software in R. Two chains were used with a burn-in period of 10,000 simulations with 100,000 simulations used in the analysis. Convergence was checked by inspection of the trace plots.

J.1.3.5 Assessing goodness of fit

To determine which model fits the data the best, the DIC was used. The difference between models in terms of DIC are compared, not the absolute values of the DICs. A DIC difference of greater than 10 between models was used to rule out the model with the higher DIC, while differences of 5–10 were considered to be substantial. The most appropriate model was not selected based on DIC alone. Other features of the model, including the scientific plausibility of the model specifications and the robustness of the results, were considered in choosing the optimal model.

J.1.3.6 Incorporating the Bayesian and cumulative ordered logit modelling in the CEA

The CEA needed to estimate the patients motor milestone achievement over time to inform treatment effectiveness following eladocagene exuparvovec and BSC. Data from the Bayesian modelling were incorporated done by taking the mean of the posterior distributions of the PDMS-2 scores in the models. These were then used to estimate individual PDMS-2 scores over time.

For the ordered logistic model, the coefficients estimated did not depend on the patient, in that it was assumed that the relationship between the predicted PDMS-2 and Bayley-III component scores and motor milestone achievement is common between patients. Each patients' motor milestone distribution was calculated using their predicted PDMS-2 score, and then the average motor milestone distribution was calculated across the patients using a fixed effects approach. As random effects were used to predict PDMS-2 scores in the Bayesian growth model, the overall two-step model approach accounts for the considerable heterogeneity between patients. It is just the relationship between the predicted PMDS-2 score and motor milestone achievement that is assumed to be the same between patients (i.e. a fixed effect).

J.1.3.7 Results: Bayesian modelling for predicting PDMS-2

As a result of the goodness-of-fit statistics for the growth models fitted to the AADC deficiency trial data for the N=28 population treated with eladocagene exuparvovec, the two best fitting models were the asymptotic model fitted with age not impacting on any coefficients and the Gompertz model where age does not impact on any of the coefficients.

The internal validation for these two models is presented in Figure 63 and shows that both models fit well for populations where there is data available up to five years post-gene-replacement therapy. For those patients with limited data, the models fit similarly across the data period, but there is some difference between the models at year five. In each case, the asymptotic model predicted higher PDMS-2 scores for these patients.

Figure 64 presents the results of the two best fitting models predicting PDMS-2 scores to ten years post-gene-replacement therapy. This data show that, for patients with up to five years of follow-up data, the Gompertz and asymptotic model specifications generated similar predictions at ten years follow-up. Internal validation (Figure 63) for patients with limited follow-up data show that the asymptotic model consistently predicts higher PDMS-2 scores at a given time.

Taken together, the Gompertz model was used in the base case and the asymptotic model was used as a scenario analysis for modelling PDMS-2 in the CEA. This is a conservative approach as the Gompertz model predicts lower PDMS-2 scores than the asymptotic model.

Figure 63. Internal validation of the two best fitting PDMS-2 growth models (N=28 population treated with eladocagene exuparvovec)

**Black line represents the observed data*

Figure 64. Extrapolation to ten years of the two best fitting PDMS-2 growth models (N=28 population treated with eladocagene exuparvovec)

**Black line represents the observed data*

J.1.3.8 Results: Bayesian modelling for predicting Bayley-III cognitive component

The results of the goodness of fit statistics for the growth models for the cognitive component of the Bayley-III fitted to the AADC deficiency trial data for the n=28 patients treated with eladocagene exuparvovec demonstrated that the Gompertz model was the worst fitting model with significantly higher DICs than the other model specifications. The two best fitting models were the asymptotic model fitted with age only depending on the alpha coefficient (representing the asymptote) and the logistic model where all the growth model parameters are assumed to be dependent on the age at treatment.

The internal validation for the asymptotic and logistic models show both models fit well for populations where there is data available up to five years post-treatment. For those patients with limited data, the models fit similarly across the data period, but there is some difference

between the models at year five. In most cases, the asymptotic model predicted higher Bayley-III cognitive component scores.

The results of the two best fitting models predicting the cognitive component of the Bayley-III score were also extrapolated to ten years post-therapy. For all patients with data on the cognitive component of Bayley-III, there are some differences in the predictions between the model specifications at ten years, with the asymptotic model consistently predicting higher scores for the cognitive component of the Bayley-III score for a given time. The asymptotic model is considered most appropriate due to the reduced number of parameters and the small sample size available with the cognitive component of the Bayley-III.

J.1.3.9 Results: Bayesian modelling for predicting Bayley-III expressive communication component

The results of the goodness of fit statistics for the growth models for the expressive communication component of the Bayley-III score fitted to the AADC deficiency trial data for the N=28 population treated with eladocagene exuparvovec. The models fitted similarly well overall. The Gompertz model with the asymptote parameter related to age was the worst fitting model with significantly higher DICs than all the other models. The two best fitting models were the asymptotic model fitted with age only depending on the alpha coefficient (representing the asymptote) and the Gompertz model where all the growth model parameters are assumed to be dependent on the age at treatment.

The internal validation for these two models shows that both models fit well for populations where there is data available up to five years post treatment. For those patients with limited data the models fit similarly across the data period and there was limited difference in all but one of the models with available data over a shorter time.The results of the two best fitting models predicting the scores from the expressive communication component of the Bayley-III score were also extrapolated to ten years post therapy. This shows that, for patients with data available up to five years the two model specifications generate similar predictions at ten years.

As for the internal validation, for the one patient with limited follow-up data there some difference between the model specifications at ten years, with the asymptotic model predicting higher expressive communication component scores from the Bayley-III for a given time. One additional patient’s prediction at ten years differs between the model specifications. This patient had a strong linear increase in their scores during the observed period. This has led to the model not reaching its inflection point by the end of the observed data point. Due to the shapes of the two models and the small number of patients in the model, this has led to the two models giving different predictions.

The Gompertz model was considered to be the most appropriate model due to the reduced number of parameters and the small sample size available with the cognitive component of the Bayley-III.

J.1.3.10 Results: Bayesian modelling for predicting Bayley-III receptive communication component

The results of the goodness of fit statistics for the growth models for the receptive communication component of the Bayley-III score fitted to the AADC deficiency trial data for the N=28 population treated with eladocagene exuparvovec demonstrated that the models fitted similarly well overall. The two best fitting models were the asymptotic model fitted with age only depending on the alpha coefficient (representing the asymptote) and the Gompertz model fitted with age only depending on the alpha coefficient (representing the asymptote).

The internal validation for these two models shows that both models fit the data equally well for all patients regardless of the available length of follow-up for the patient.

The results of the two best fitting models predicting the scores from the receptive communication component of the Bayley-III were also extrapolated to ten years post therapy. For all patients, the two model specifications generate similar predictions at ten years.

Due to the models fitting very similarly across the population and the non-significant differences in their DICs, the asymptotic model was considered most appropriate due to marginally smaller DIC and the small sample size available with the cognitive component of the Bayley-III.

J.1.3.11 Results: Cumulative ordered logit modelling to predict motor milestones

When including the cognitive component of the Bayley-III score in the model, the coefficient generated was negative. This implies that, as a patient's Bayley-III cognitive component score increases, the likelihood of that patient reaching a higher motor milestone is reduced. This is inconsistent with the positive correlation between Bayley-III cognitive scores and motor function as outlined above. Similar results occur in the model that includes PDMS-2 and Cognitive, Expressive Communication and Receptive Communication components of the Bayley-III, whereby the expressive communication component of the Bayley-III has a negative impact on the likelihood of meeting higher motor milestones (i.e. worse Bayley-III component score equates to better motor milestones).

The counterintuitive results combined with the small sample size for the Bayley-III components means that Bayley-III component scores generate greater uncertainty in the prediction of motor milestones than using PDMS-2 score alone. Thus, the cumulative ordered logit model in the CEA uses PDMS-2 as the only covariate. Table 132 presents the median and 95% credible interval estimates for the cumulative ordered logistic models, using PDMS-2 scores as a covariate, used to predict a patient's motor milestone achievement.

Table 132. Median and 95% credible interval estimates for the cumulative ordered logit models to estimate motor milestones achievement (N=28 population)

	PDMS-2 only
N included	28
Coefficients	
PDMS-2	0.059 (0.047, 0.070)
θ	
θ_1	3.983 (3.049, 4.973)
θ_2	5.623 (4.487, 6.818)
θ_3	9.867 (8.017, 10.291)
θ_4	12.516 (10.291, 14.899)

Figure 65 presents the results of the internal validation of the cumulative ordered logit model with PDMS-2 as a covariate using the observed PDMS-2 values as inputs. This shows that the model validates well across all motor milestone stages and over all time points. The uncertainty around the predicted values increases over time due to the attrition of the observed population in the trial meaning that the observations are made over a smaller number of patients and hence are more uncertain. This is in comparison to the predicted values estimated using the data from the whole population.

Figure 66 presents the results of the cumulative ordered logit model with PDMS-2 as a covariate extrapolated to ten years post therapy. This indicates that the distribution of patients between motor milestones has stabilised by approximately five years post-therapy. This is supported by the predictions from the growth model for PDMS-2 (Figure 63), which indicate that PDMS-2 scores approach plateau at year five post-gene-replacement therapy.

Figure 65. Internal validation of the cumulative ordered logit model estimated with PDMS-2 as a covariate (N=28)

Figure 66. Predictions of the cumulative ordered logit model to ten years post therapy estimated with PDMS-2 as a covariate (n=28)

J.1.3.11 Rationale for using PDMS-2 only to predict motor milestones in the CEA

The aim of the Bayesian and cumulative ordered logit modelling was to predict patient motor milestone achievement over time based on observed clinical trial data, and to account for the small sample size and heterogeneous outcomes in trials for eladocagene exuparvovec. In the first stage, a patients PDMS-2 and Bayley-III scores were estimated through Bayesian growth models. These scores were then used in a cumulative ordered logit model to estimate a patient's motor milestone achievement.

In terms of PDMS-2 the best fitting models were the asymptotic and Gompertz models with age not impacting any of the parameters. All models validated well across the observed data and generated consisted predictions to ten years post therapy, with some differences between the models in terms of the predicted values for those patients with limited data. Non-convergence was an issue, as identified by trace plots. This was not unexpected due to the small amount of data and the large demands placed upon it in the model specifications.

Analysis was carried out on the best fitting models for components of the Bayley-III instrument. For these components it was possible to identify models that validated well, despite the Bayley-III score only being collected for a small number of patients in the trials.

PDMS-2 was found to be a significant predictor of motor milestone achievement. The inclusion of Bayley-III components models led to a smaller sample size and counterintuitive results that indicated that lower Bayley-III scores correlated with higher motor milestone achievement.

Due to these counterintuitive conclusions and the high correlation between PDMS-2 and Bayley-III component scores, Bayley-III components were not considered appropriate for inclusion in the cumulative ordered logit model. The optimal model for estimating motor milestones in the CEA was the cumulative ordered logit model with PDMS-2 as a covariate. This model validated well (Figure 65).

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 133: Disaggregated results: summary of QALY gain by health state

Health state	QALY eladocagene exuparvovec	QALY BSC	Increment	Absolute increment	% absolute increment
No-motor function	[redacted]	5.37	[redacted]	[redacted]	-
Full-head control	[redacted]	0.01	[redacted]	[redacted]	-
Sitting unassisted	[redacted]	0.28	[redacted]	[redacted]	-
Standing with support	[redacted]	0.00	[redacted]	[redacted]	-
Walking with assistance	[redacted]	0.61	[redacted]	[redacted]	-
Total	[redacted]	6.28	[redacted]	[redacted]	100%

Abbreviations: BSC – best supportive care; QALY – quality-adjusted life year.

Table 134: Disaggregated results: summary of costs by health state

Health state	Cost eladocagene exuparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
No-motor function	£[redacted]	£[redacted]	£[redacted]	£[redacted]	-
Full-head control	£[redacted]	£[redacted]	£[redacted]	£[redacted]	-
Sitting unassisted	£[redacted]	£[redacted]	£[redacted]	£[redacted]	-
Standing with support	£[redacted]	£[redacted]	£[redacted]	£[redacted]	-
Walking with assistance	£[redacted]	£[redacted]	£[redacted]	£[redacted]	-
Total	£[redacted]	£[redacted]	£[redacted]	Total absolute increment	100%

Abbreviations: BSC – best supportive care

Table 135: Summary of predicted resource use by category of cost

Item	Cost eladocagene exuparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
Drug acquisition and administration-related costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Disease management	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Follow-up visits	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Technical procedures	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Medical procedures	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Adverse event	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Dyskinesia	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Pneumonia	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Gastrointestinal disorders	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Gastroenteritis	£[redacted]	£[redacted]	£[redacted]	£[redacted]	
Total	£[redacted]	£[redacted]	£[redacted]	Total absolute increment	100%

Abbreviations: BSC – best supportive care

Appendix K: Price details of treatments included in the submission

K1.1 Price of intervention

Please see Table 136 for information on the price details of the intervention, including concomitant medications.

Table 136: Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	Patient access scheme price
Price details of the technology						
Eladocagene exuparvovec	Solution for infusion	2.4×10^{11} vector genomes/0.5mL solution	Single dose vial	£[redacted]	Data on File	£[redacted]
Price details of symptomatic medications that may be used following treatment with eladocagene exuparvovec*						
Pramipexole	Tablet	180 mg	100	£13.92	BNF[113]	-
Ropinirole	Tablet	2 mg	84	£21.51	BNF[113]	-
Rotigotine	Transdermal patch	4 mg	28	£123.60	BNF[113]	-
Bromocriptine	Tablet	10 mg	100	£74.99	BNF[113]	-
Tranylcypromine	Tablet	10 mg	28	£429.61	BNF[113]	-
Selegiline	Tablet	10 mg	100	£32.23	BNF[113]	-
Pyridoxine Hydrochloride	Tablet	10 mg	60	£0.77	BNF[113]	-
Trihexyphenidyl hydrochloride	Tablet	2 mg	84	£5.51	BNF[113]	-
Diazepam	Tablet	10 mg	28	£1.06	BNF[113]	-
Melatonin	Tablet	3 mg	30	£19.75	BNF[113]	-
Clonidine	Tablet	0.1 mg	100	£8.04	BNF[113]	-
Levodopa	Tablet	200 mg	30	£20.79	BNF[113]	-
Folic acid	Tablet	5 mg	28	£1.03	BNF[113]	-
Ensure Plus Advance	Liquid	1 ml	220	£2.20	BNF[113]	-
Colecalciferol	Capsule	800 mg	30	£2.95	BNF[113]	-

**Please note: symptomatic treatment use post-gene therapy is highly individualised based on specific symptoms experienced by the patient.*
Abbreviations: BNF – British National Formulary; mg - milligrams

K1.2 Price of comparators and subsequent treatments

Please see Table 137 for information on the price details of symptomatic treatments used as part of BSC.

Table 137: Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	Patient access scheme price
Pramipexole	Tablet	180 mg	100	£13.92	BNF[113]	-
Ropinirole	Tablet	2 mg	84	£21.51	BNF[113]	-
Rotigotine	Transdermal patch	4 mg	28	£123.60	BNF[113]	-
Bromocriptine	Tablet	10 mg	100	£74.99	BNF[113]	-
Tranylcypromine	Tablet	10 mg	28	£429.61	BNF[113]	-
Selegiline	Tablet	10 mg	100	£32.23	BNF[113]	-
Pyridoxine Hydrochloride	Tablet	10 mg	60	£0.77	BNF[113]	-
Trihexyphenidyl hydrochloride	Tablet	2 mg	84	£5.51	BNF[113]	-
Diazepam	Tablet	10 mg	28	£1.06	BNF[113]	-
Melatonin	Tablet	3 mg	30	£19.75	BNF[113]	-
Clonidine	Tablet	0.1 mg	100	£8.04	BNF[113]	-
Levodopa	Tablet	200 mg	30	£20.79	BNF[113]	-
Folic acid	Tablet	5 mg	28	£1.03	BNF[113]	-
Ensure Plus Advance	Liquid	1 ml	220	£2.20	BNF[113]	-
Colecalciferol	Capsule	800 mg	30	£2.95	BNF[113]	-

Abbreviations: BNF – British National Formulary; mg - milligrams

Appendix L: Checklist of confidential information

Please refer to the separate Appendix L file provided as part of the submission package.

Appendix M: Additional clinical information

Table 138: AADC-010: Percentile of body weight shift from baseline to Month 12 (n=10)

	Percentile at Month 12, n/m (%)								
Percentile at baseline	**<=3**	**>3-<=15**	**>15-<=25**	**>25-<=50**	**>50-<=75**	**>75-<=85**	**>85-<=97**	**>97**	**Total**
<=3									
>3-<=15									
>15-<=25									
>25-<=50									
>50-<=75									
>75-<=85									
>85-<=97									
>97									
Total									

Abbreviations: m – Total number of subjects with body weight data; n – Number of subjects in each percentile

Figure 67: AADC-CU/1601: Floppiness by timepoint (ITT population; N=8)

Abbreviations: ITT – Intent-to-treat

Figure 68: AADC-CU/1601: OCG episodes by timepoint (ITT population; N=8)

Abbreviations: ITT – Intent-to-treat; OCG – Oculogyric crisis

Figure 69: AADC-CU/1601: limb dystonia by timepoint (ITT population) (n=8)

Abbreviations: ITT – Intent-to-treat

Figure 70: AADC-CU/1601: Stimulus-provoked limb dystonia (ITT population; N=8)

Abbreviations: ITT – Intent-to-treat

Table 139: AADC-CU/1601: Putaminal-specific F-DOPA PET uptake (ITT; N=8)

PET parameter	N	Data type	Timepoint	Mean (SD)	LS mean (SE)	95% CI of LS mean
Specific uptake	8	Raw	BL	[redacted]	[redacted]	[redacted]
	4	CFB	Month 6	[redacted]	[redacted]	[redacted]
	4	CFB	Month 12	[redacted]	[redacted]	[redacted]
	2	CFB	Month 60	[redacted]	[redacted]	[redacted]
	2	CFB	After month 60 [a]	[redacted]	[redacted]	[redacted]

Abbreviations: BL – Baseline, CFB – Change from baseline; CI – Confidence interval; ITT – Intent-to-treat; LS – Least squares; SD – Standard deviation; SE – Standard error

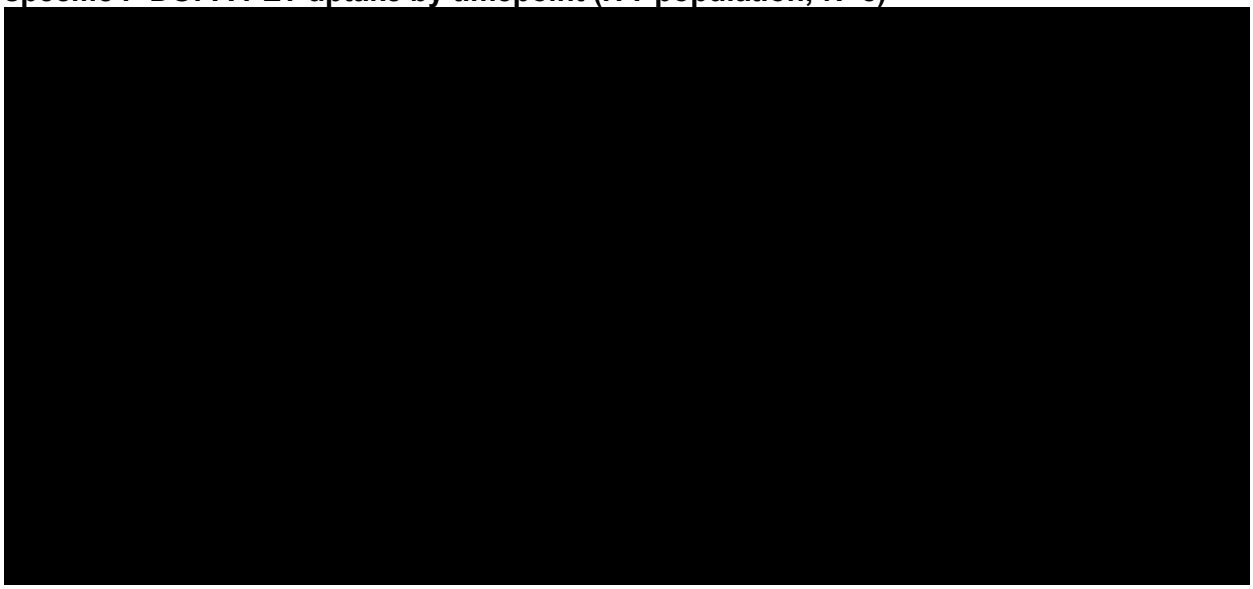
[a] – For these patients, PET data were the only data obtained after month 60 as this was the only time when the patients were able to obtain an imaging examination.

Table 140: AADC-CU/1601: Putaminal-specific F-DOPA PET uptake (ITT; N=8)

Fixed effect	Numerator DF	Denominator DF	F-value	P-value
Visit	[redacted]	[redacted]	[redacted]	[redacted]
Age (in months at gene-replacement therapy)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DF – Degrees of freedom; ITT – Intent-to-treat

Figure 71: AADC-CU/1601: Least squares means and standard errors for putaminal-specific F-DOPA PET uptake by timepoint (ITT population; N=8)



Abbreviations: ITT – Intent-to-treat

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Summary of Information for Patients (SIP)

June 2022

File name	Version	Contains confidential information	Date
ID3791_eladocagene exuparvovec for AADC_SIP form v1.0_17May2022_FINAL	1.0	No	1 June 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response:
• Eladocagene exuparvovec (Upstaza®)[1]

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
• Upstaza is indicated 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[1]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
• Eladocagene exuparvovec received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 19 May 2022 and is expected to be granted a marketing authorisation under “exceptional circumstances” by the European Medicines Agency (EMA) and Medicines and healthcare products Regulatory Agency (MHRA) in the coming months. The EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU[2]. The MHRA regulates the medicines, medical devices and blood components for transfusion in the UK.[3] Exceptional circumstances relates to the rarity of the disease meaning it is not possible to obtain complete information on the product.[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

- PTC has provided financial support to Metabolic Support UK, in the form of a grant, to support its activities in the UK. Total payments to Metabolic Support UK have been £15,000. PTC has not made any payments to The AADC Research Trust. PTC acquired Agilis (a gene therapy company) in 2018, through which it also acquired the rights to Upstaza (eladocagene exuparvovec) and payments to The AADC Research Trust may have been made by Agilis prior to or during the period of the company's acquisition by PTC.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

AADC deficiency is an ultra-rare, severely disabling and life-shortening genetic condition with first symptoms presenting in early childhood:

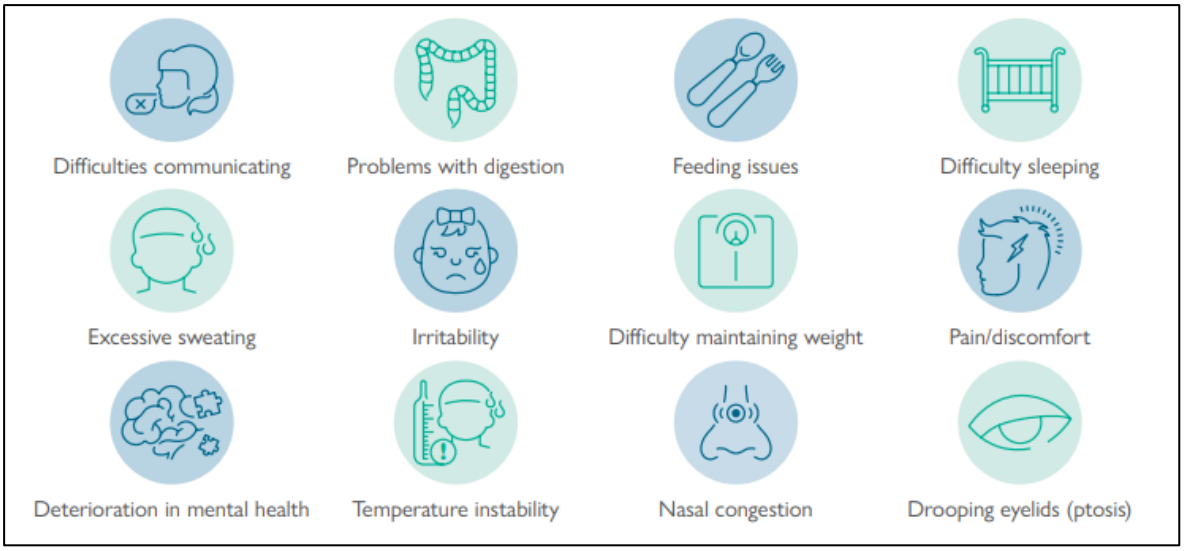
- AADC deficiency is a rare genetic disorder that affects the brain, causes weak muscle tone, and affects how a child develops. It is caused by a mutation in the dopa decarboxylase (DDC) gene, leading to deficient production of the AADC enzyme and therefore leads to a lower level/no neurotransmitters (chemical messengers in the brain).[4]
- AADC deficiency is an underreported condition, which makes estimating global prevalence (total number of patients) very challenging. From a large natural history database, 237 cases of AADC deficiency have been described in the science literature globally.[5]
- In the UK, there are 9 patients with AADC deficiency, equating to a prevalence of approximately 1 in every 7.5 million people. UK clinical experts estimate that very few patients will be diagnosed over the next 5 years.[6]
- Children with severe AADC deficiency achieve no baby development milestones and demonstrate a wide variety of symptoms, including floppiness (decreased muscle tone), poor head control, motor dysfunction, developmental delay, cognitive and emotional issues, movement disorders, and seizure-like eye movements (oculogyric crises; OGC).[4,7]
- Children with severe AADC deficiency (defined in 2017 clinical guidelines as no or very limited major motor developmental milestones and full dependence)[4] have very early death. While published survival estimates are limited, it is widely reported that patients with severe AADC deficiency live for less than 10 years due to severe symptoms (such as motor dysfunction and secondary complications).[4,8,9]
- UK clinical experts estimate that patients with severe AADC deficiency do not live into their teenage years or beyond theirs 20s.[6]

AADC deficiency is associated with a considerable burden to patients:

- AADC deficiency causes severe disability and suffering from the first months of life as it affects every aspect of life – physical, mental and behavioural.[4,10–12]
- The average age that children with AADC deficiency show signs and symptoms is around 2.7 months.[4]
- The burden on infants and children with severe AADC deficiency is major, impacting development, motor skills (ability to hold head up, sit unsupported, stand or walk), growth, function, cognitive and language skills, and behaviour.[4]

- Patients experience severe and excessive crying as well as regular, distressing and life-threatening episodes of OGC lasting for hours at a time.[13] OCG is a medical term describing episodes where the eyes suddenly roll upwards.[14]
- The physical burden of AADC deficiency is extreme as most children will never be able to hold their head up, sit by themselves, stand, or speak.
- Floppiness, which is referred to medically as hypotonia (decreased muscle tone), is one of the main symptoms of AADC deficiency.[4]
- Many children are reliant on feeding tubes and/or breathing support to survive.[10,15–17]
- The social burden and subsequent mental and behavioural detrimental effects stem from children with severe AADC deficiency being unable to move and communicate, meaning they will never be able to play with toys or go to school and interact with classmates.[10,15–17]
- The wide-ranging burden of severe AADC deficiency is demonstrated in Figure 1 below.[18]

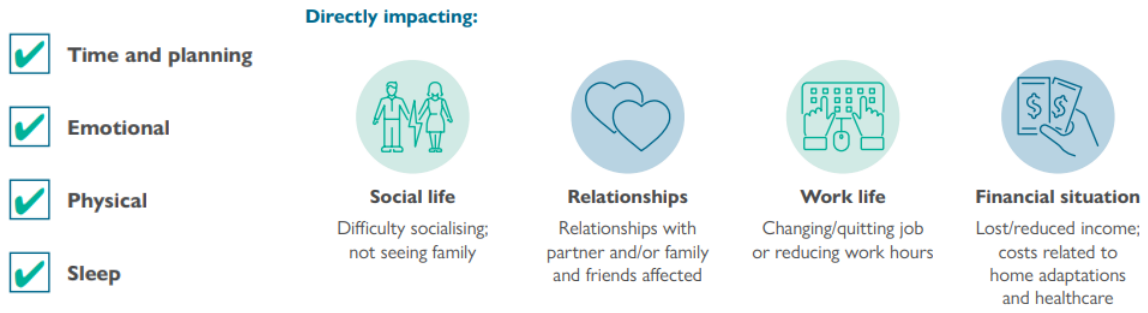
Figure 1: The patient burden of severe AADC deficiency[11,18–20]



There is a substantial burden for families/caregivers of patients with severe AADC deficiency.

- Caring for a child with AADC deficiency impacts the whole family physically, emotionally, and financially, as shown in Figure 2.
- Caring for children with severe AADC deficiency requires constant, 24-hour, one-to-one support with all aspects of carrying out daily living tasks, such as getting dressed, bathing, eating, toileting and simply being able to move.[15,16]
- Caregivers spend an average of 13 hours (8-20 hours) per day on practical and emotional care for their child with severe AADC deficiency and spend a mean of 15 hours (7-33 hours) per week on administrative tasks such as planning activities or travelling to/attending appointments related to their child's disease.[16]
- Caregiving also impacts work productivity, with 75% of caregivers reporting that they stopped working or reduced their working hours in order to care for their child with severe AADC deficiency.[16]
- Caregivers have little time to themselves (e.g., for exercise, or even to shower) and this negatively affects their ability to carry out household tasks, go to work and attend social events.[16]
- Being a caregiver to a child with severe AADC deficiency has a substantial impact on emotional wellbeing, with caregivers reporting depression, anxiety, and fear for the future.[21] It has a substantial impact on physical wellbeing, with caregivers reporting back and neck pain from lifting and carrying their child.[21]
- Caregiver quality of life (QoL) is further impacted through sleep deprivation due to feeling the need to continuously check on their child throughout the night or due to anxiety and worry.[21]

Figure 2: The caregiver burden of severe AADC deficiency[21]



2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

- AADC deficiency diagnoses are made in patients with suspicious clinical symptoms, including unexplained floppiness, movement disorders (especially OGC), development delay, and autonomic symptoms.[4,7]
- Diagnosis of AADC deficiency requires a positive result from 2 or more of the following tests:[4]
  - Cerebral spinal fluid (CSF) neurotransmitter metabolite panels: neurotransmitters allow cells in the nervous system to communicate. This test measures the levels of different compounds (metabolites) involved in the making of neurotransmitters.
  - Genetic testing: to look more closely at the DDC gene.
  - Plasma enzyme assay: this measures the activity of the AADC enzyme in the blood, which is reduced in patients with AADC deficiency.
- AADC deficiency CSF testing for neurotransmitter disorders is carried out in the UK at the designated national referral centre at the Neurometabolic Unit at the National Hospital in London. Paediatricians are well educated on its availability.
- Genetic confirmation is required to confirm eligibility for eladocagene exuparvovec. Genetic testing is usually conducted in the UK to confirm a diagnosis of AADC deficiency. No new diagnostic tests will therefore be required with the introduction of eladocagene exuparvovec in the UK.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

Current management:

- There are currently no licensed treatments that address the underlying cause of AADC deficiency, and no UK or NICE clinical guidelines or treatment pathways exist.
- Current treatment options for patients with AADC deficiency focus on managing symptoms only[4,22,23] and the choice of therapy varies based on clinician preference.
- To treat the symptoms of AADC deficiency, several different medications can be given. In general, the first treatments given for the disorder are:[4]
    - Dopamine agonists, which mimic the actions of dopamine in the brain,
    - Inhibitors of monoamine oxidase to increase the levels of dopamine and serotonin in the brain,
    - Pyridoxine, or vitamin B6, to increase the action of the AADC enzyme.
- Treatments tend to only be effective when the specific symptoms they treat are mild. Patients with severe AADC deficiency often do not see an improvement in their condition despite available therapies.[4]
- With current management, 97% of patients with severe AADC deficiency fail to achieve any motor milestones, remain bedridden for their lifetime, and rarely survive into their teens.[4,10,24]

Eladocagene exuparvovec (Upstaza®) will become the standard of care:

- Eladocagene exuparvovec is a one-time gene therapy that can be used in patients aged 18 months and older with severe AADC deficiency.[1]
- Eladocagene exuparvovec works by replacing the faulty gene responsible for AADC deficiency, in turn restoring the production of essential neurotransmitters such as dopamine.
- Eladocagene exuparvovec is a one-time gene replacement therapy that involves direct delivery of the therapy to a region of the brain known as the putamen. The putamen is where the AADC enzyme is made. Eladocagene exuparvovec will be the first approved gene therapy to be administered directly to the brain.
- If eladocagene exuparvovec is approved, it will be the first and only licensed, effective, disease-modifying treatment and the only treatment to directly address the genetic cause of AADC deficiency. It offers much-needed hope to children with AADC deficiency and their family caregivers.
- Eladocagene exuparvovec is expected to become the new standard of care (accepted by medical experts) and is expected to be made available to all eligible patients given the absence of any other options.
- Following treatment with eladocagene exuparvovec, patients may be prescribed treatments to ease symptoms on an individual patient basis.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

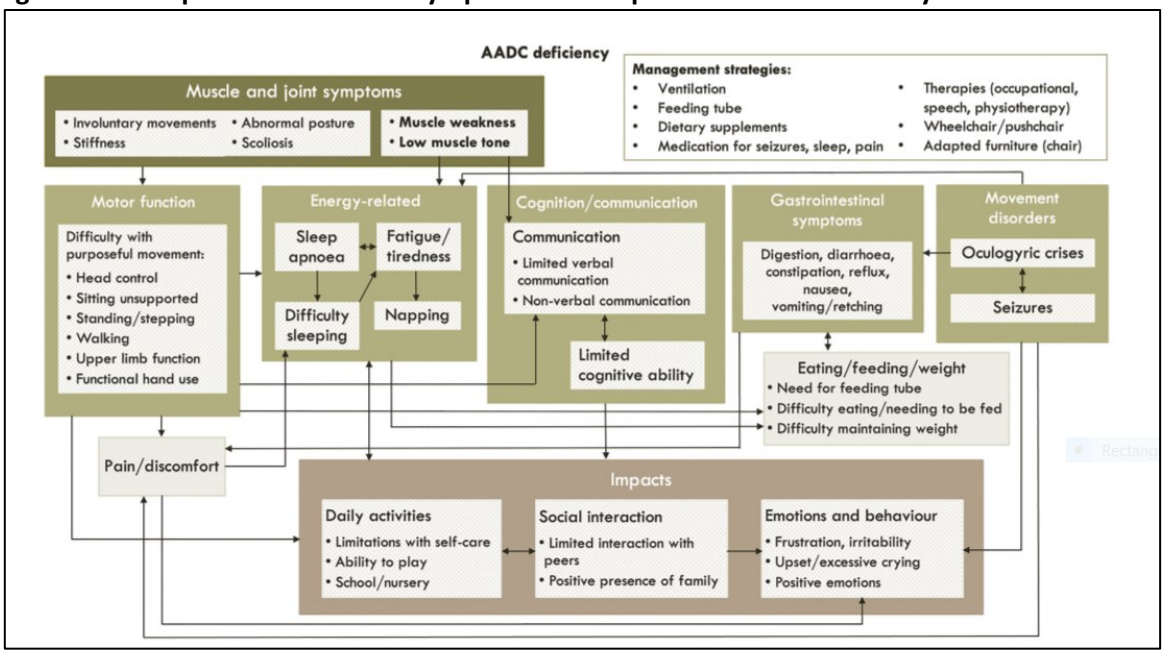
In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Patients

- Very little PBE has been collected in children with severe AADC deficiency due to the severe and ultra-rare nature of the disease and young age of patients. Children with severe AADC deficiency are unable to communicate and their symptoms are too severe to allow them to input into scientific research. Most PBE in AADC deficiency, therefore, is based on information provided by caregivers of patients with AADC deficiency.
- Figure 1 highlights the patient burden of severe AADC deficiency. Symptoms and functional impairments impact patients' daily activities, social interaction, emotions, and behaviour, demonstrating the large burden of AADC deficiency.[18]
- Due to the nature of the disease and its associated symptoms, most patients require lifelong care and are reliant on caregivers for all aspects of their daily lives.[18]
- Patients suffer from physical and emotional symptoms that indicate profound distress and quality of life impairment, including sleep disturbance, pain, discomfort, seizures, excessive crying, irritability, and general unease and unhappiness.[4,13,25]
- Figure 3 below shows the more severe and direct impacts of AADC deficiency at the top of the flow chart, down to the more indirect impacts at the bottom.

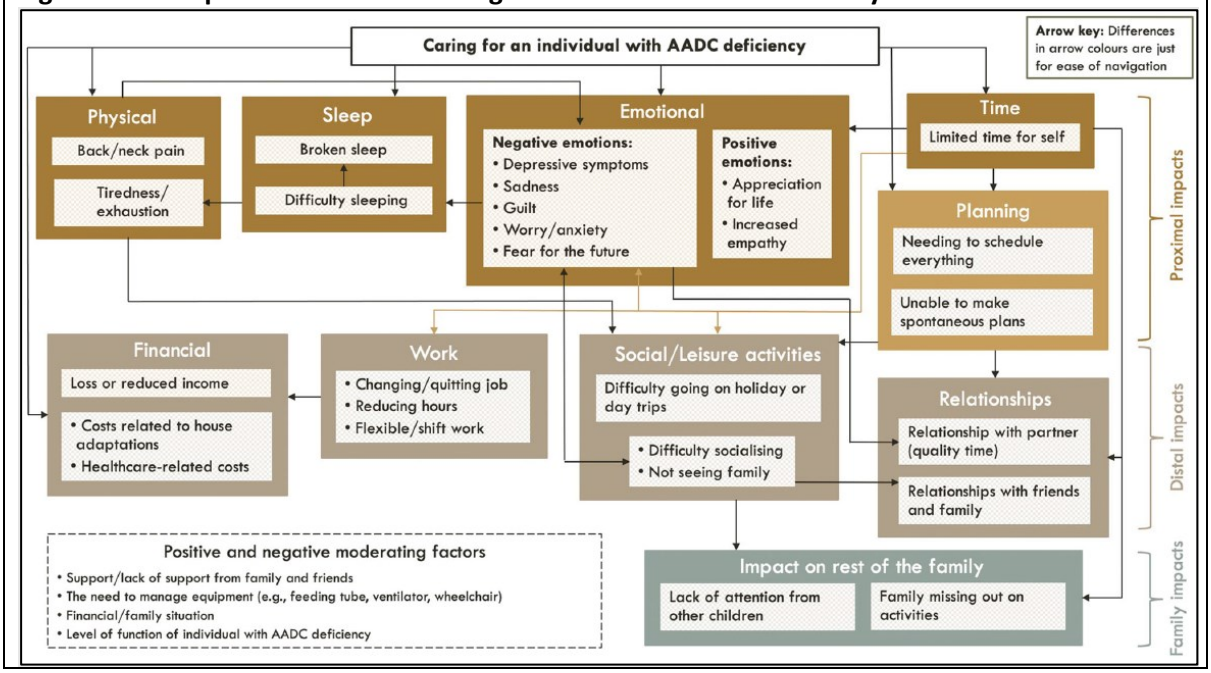
Figure 3: Conceptual model of the symptoms and impacts of AADC deficiency[26]



Caregivers

- Figure 2 highlights the challenges faced by caregivers of children with severe AADC deficiency.
- Family caregivers report spending an average of 13 hours (8-20h) per day on practical and emotional care for their child with AADC deficiency.
- Caregiver hours can be spent washing and bathing, feeding, administering medication, ensuring physiotherapy exercises are carried out, managing equipment related to AADC deficiency, as well as providing emotional support and care.[16,21]
- Family caregivers report that caring for a child with AADC deficiency causes depressive symptoms, sadness, and anxiety.[21]
- Family caregivers report giving up employment and social activities to care for their child with AADC deficiency.[21]
- The caregiver impact of AADC deficiency is provided in Figure 4.

Figure 4: Conceptual model of the caregiver burden of AADC deficiency



SECTION 3: The treatment

3a) How does the new treatment work?

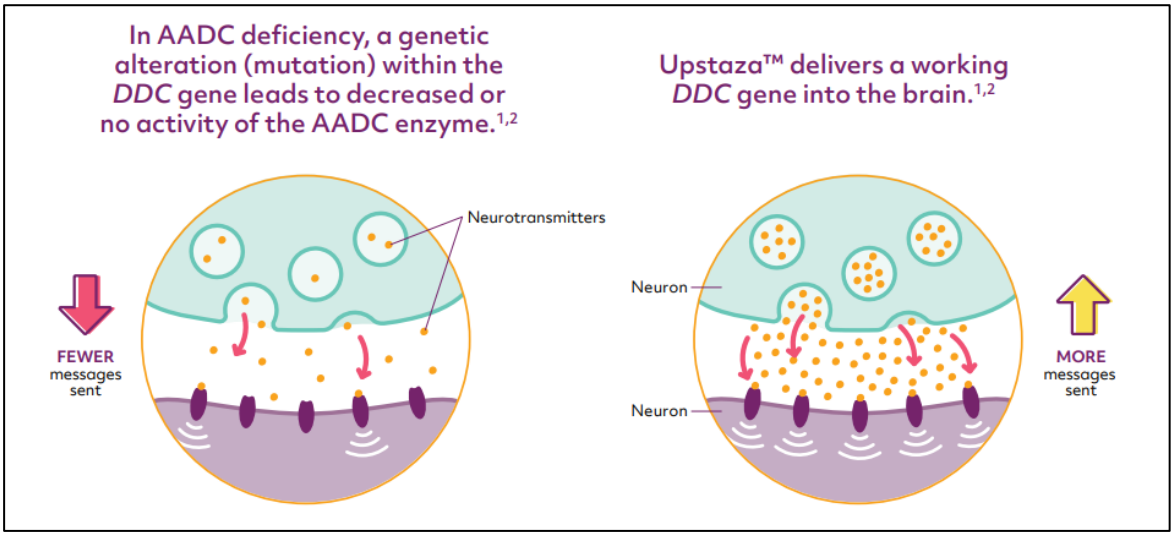
What are the important features of this treatment?
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

- In AADC deficiency, a genetic alteration (mutation) within the DDC gene leads to decreased or no activity of the protein called aromatic L-amino acid decarboxylase (AADC). This protein is essential to make certain substances that the body's nervous system needs to work properly.
- The condition prevents development of the child's nervous system, which means that many of the body's functions do not develop correctly during childhood, including movement, eating, breathing, speech and mental ability.
- Eladocagene exuparvovec is a gene replacement therapy that restores AADC activity. It is given by infusion (drip) into an area of the brain called the putamen, where AADC is made. The surgery is given at specialised treatment centres by a qualified neurosurgeon.[1]
- Eladocagene exuparvovec restores the use of the AADC enzyme in the brain, resulting in production of dopamine and other essential substances that the nervous system needs to control motor function, development, and other symptoms associated with AADC deficiency.[1]

Figure 5: Administration of Eladocagene exuparvovec (Upstaza®)



- Restoring the production of dopamine and other neurotransmitters in patients with AADC deficiency results in achievement of key motor milestones (including head control, sitting unassisted, standing with support, and walking with assistance), and sustained improvements in motor function, OGCs, body weight, cognition, language, and muscle tone.
- Eladocagene exuparvovec provides potentially life-long benefits from a one-time administration, with children continuing to show benefits at least five years after receiving the gene therapy (and up to 9 years).[27]
- Eladocagene exuparvovec is highly innovative as it addresses the underlying genetic cause of AADC deficiency and is the first and only disease-modifying therapy, unlike current symptomatic treatment options.
- Eladocagene exuparvovec provides much-needed hope and life-changing benefits to patients and caregivers. For an example of the life-changing benefits of eladocagene exuparvovec, please see videos of patients before and after treatment in Tai *et al.,* 2022[28] and in a patient video provided to the EMA as part of the appraisal process (see reference 29).[29]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.
If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.
If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

- Eladocagene exuparvovec is a gene therapy that is not used in combination with any other therapies and is expected to deliver life-long benefits.
- It is possible that some patients may need other drugs and treatments to help manage symptoms of AADC deficiency after eladocagene exuparvovec gene therapy. Treatment will be on an individual basis depending on the specific symptoms experienced by the patient.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

- Eladocagene exuparvovec is administered via a one time surgical procedure in which the functioning *DDC* gene is administered directly into the brain. The neurosurgical procedure is well-established in the UK and is expected to take 6-8 hours. Patients are monitored closely before and after the surgery.
- Eladocagene exuparvovec is given at a dose of $1.8x10^{11}$ vector genomes.
- After the one time surgery, there is no further requirement for eladocagene exuparvovec therapy and patients are expected to receive lifelong benefits.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response: Eladocagene exuparvovec has been studied in three clinical trials. Information on each study is provided below.

AADC-010

- **Title**: A phase 1/2 clinical trial for treatment of AADC deficiency using AAV2-hAADC (eladocagene exuparvovec)
- **Objective**: 1) To understand if expression of the gene transferred by eladocagene exuparvovec can facilitate dopamine production to improve patient motor function, and 2) to ensure the safety the gene therapy
- **Location**: Taiwan
- **Population**: Children aged 2+ years with AADC deficiency
- **Patient group size**: N=10
- **Comparators**: None. Due to the severe and ultra-rare nature of AADC deficiency, AADC-010 was an open-label (i.e. not blinded), single arm trial
- **Inclusion criteria**: 1) Confirmed diagnosis of AADC; 2) Classical clinical characteristics of AADC deficiency, such as OGC, floppiness, and developmental retardation; 3) 2+ years of age or a head circumference big enough for surgery
- **Exclusion criteria**: 1) Patient had significant brain structure abnormality; 2) Patient had health or neurological concerns that may have increased the risk of surgery; 3) Patient was taking medications that may affect the study outcomes
- **Primary efficacy endpoint**: The proportion of patients achieving key motor milestones, determined using PDMS-2 at 5 years following gene therapy.
- **Completion date:** 18 October 2020

AADC-011

- **Title**: A clinical trial for treatment of AADC deficiency using AAV2-hAADC (eladocagene exuparvovec) - an expansion
- **Objective**: To evaluate the safety and efficacy of eladocagene exuparvovec in children with AADC deficiency for a period of up to 1 year after study drug administration in order to: 1) give patients who were not enrolled in the Phase 1/2 trial (i.e. AADC-010) an opportunity for treatment, 2) increase experience in gene therapy for AADC deficiency, 3) to slightly increase the dose in patients aged <3 years
- **Location**: Taiwan
- **Population**: Children aged 2–6 years with AADC deficiency
- **Patient group size**: N=12 (N=3 treated with $1.8x10^{11}$ vg dose; N=9 treated with $2.4x10^{11}$ vg).

- **Comparators**: None. Due to the severe and ultra-rare nature of AADC deficiency, AADC-011 was an open-label, single arm trial
- **Inclusion criteria**: 1) Confirmed diagnosis of AADC deficiency; 2) Classical clinical characteristics of AADC deficiency, such as OGC, floppiness, and developmental retardation; 3) 2+ years of age or had a head circumference big enough for surgery; 4) Not older than 6 years prior to gene therapy
- **Exclusion criteria**: 1) If the patient had significant brain structure abnormality as determined by the investigator; 2) Any health or neurological concerns that may have increased the risk of surgery; 4) If the patient was taking any medications that may affect the outcome of the trial
- **Primary efficacy endpoint**: Proportion of patients achieving key motor milestones at 1 year following gene therapy, as determined using PDMS-2.
- **Completion date:** 30 January 2022

AADC-CU/1601

- **Title:** Compassionate use treatment with eladocagene exuparvovec in patients with AADC deficiency
- **Objectives:** 1) To evaluate the safety and long-term benefits of administration of eladocagene exuparvovec in patients with AADC deficiency, 2) to collect data from patients who received humanitarian assistance treatment of eladocagene exuparvovec, and 3) to observe the safety and efficacy for up to 60 months (5 years) after treatment
- **Location**: Taiwan
- **Population**: Children aged 2+ years with AADC deficiency
- **Patient group size**: N=8
- **Comparators**: None. Due to the severe and ultra-rare nature of AADC deficiency, AADC-CU/1601 was an open-label, single arm trial.
- **Inclusion criteria**: 1) Confirmed diagnosis of AADC deficiency; 2) Classical clinical characteristics of AADC deficiency, such as OGC, floppiness, and developmental delay; 3) 2+ years of age
- **Exclusion criteria**: 1) Health or neurological concerns that may have increased the risks associated with surgery; 2) Patient is taking any medications that may affect the trial; 3) Patient has severe allergic reaction to the components of the therapy.
- **Primary efficacy endpoint**: The proportion of patients who achieved key motor milestones at 60 months following gene therapy, as assessed using the Peabody Developmental Motor Scales Second Edition scale (PDMS-2; composed of six sub-tests that measure interrelated motor abilities of children from birth to five years of age). The proportion of patients at each motor milestone at Month 12 and 24 was provided as supportive analyses.
- **Completion date:** 7 August 2018

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

- Due to the severe and ultra-rare nature of AADC deficiency, all clinical trials were open-label, single-arm trials for ethical reasons meaning there is no head-to-head data for eladocagene exuparvovec treatment versus current best supportive care.
- Efficacy results reported in clinical studies are compared to baseline (i.e. before the patient received eladocagene exuparvovec).[1,28]

- In all three trials, following gene therapy, subjects demonstrated significant clinical benefits with sustained improvements in motor function.[1,28]
- Patients continue to demonstrate significant benefits in motor function at 9 years following gene therapy, highlighting the sustained benefit of eladocagene exuparvovec.

AADC-010

- **Primary efficacy endpoint (motor milestones):** Patients with AADC deficiency experienced rapid and durable improvements in motor milestones following treatment with eladocagene exuparvovec.[30]
    - At baseline, all patients had no motor function.
    - At Month 12 following treatment, some patients achieved full head control and could sit unassisted.
    - At Month 60 following eladocagene exuparvovec, some patients achieved full head control, could sit unassisted, could stand with support, and could walk with assistance.
    - The proportion of patients achieving each motor milestone increased over time.
    - This indicates that the benefits of eladocagene exuparvovec start within the first year after treatment and improvements continue for an extended period up to at least 60 months after treatment.
- **Improvements across all outcomes related to AADC deficiency**: patients with AADC deficiency experienced rapid and durable improvements in all outcomes measured in the study, including:[30]
    - Motor function (as measured by PDMS-2).
    - Development and motor function (as measured by AIMS).
    - Development and cognition (as measured by Bayley-III).
    - The incidence of floppiness and other symptoms decreased after treatment.
    - The proportion of time spent experiencing OGC episodes was sustainably reduced after gene therapy.

AADC-011

- **Primary efficacy endpoint (motor milestone improvement):**[31]
    - At baseline, all patients had no motor function.
    - At Month 12, some patients achieved full head control and could sit unassisted.
    - All patients demonstrated emerging and/or mastery of motor skills.
- **Improvements across all outcomes related to AADC deficiency**: patients with AADC deficiency experienced rapid and durable improvements in all outcomes measured in the study, including:[31]
    - Motor function (as measured by PDMS-2)
    - Development and motor function (as measured by AIMS)
    - Floppiness, OGC, and other symptoms decreased as early as 3 months and continued for 1 year after treatment.

AADC-CU/1601

- **Primary efficacy endpoint (motor milestones):** patients with AADC deficiency experienced rapid and durable improvements in motor milestones following treatment with eladocagene exuparvovec.[32]
    - At baseline, all patients had no motor function (no head control and floppiness).
    - At month 12 following eladocagene exuparvovec, some patients achieved full head control and some could sit unassisted.
    - At month 60 following eladocagene exuparvovec, some patients had full head control, some could sit unassisted, and some were able to stand with support.
    - The proportion of patients achieving each motor milestone increased over time.
    - This indicates that the benefits of eladocagene exuparvovec start within the first year after treatment and improvmements continue for an extended period up to at least 60 months after treatment.

- A natural history database shows that only 3% of patients with severe AADC deficiency achieve full head control without gene therapy.[33]

- **Improvements across all outcomes related to AADC deficiency**: patients with AADC deficiency experienced rapid and durable improvements in all outcomes measured in the study, including:[32]
  - Motor function (as measured by PDMS-2).
  - Development and motor function (as measured by Alberta Infant Motor Scale (AIMS)).
  - Development and cognition (as measured by Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT)).
  - The number of patients with floppiness, seizure-like OGC episodes, limb dystonia (involuntary contraction of muscles), and stimulus-provoked dystonia decreased at one year after eladocagene exuparvovec infusion.
  - No patients required new treatment with a dopaminergic agent, which is a widely used symptomatic treatment in patients with no motor function.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Patient-related quality of life impact of eladocagene exuparvovec:

- Quality of life data, including EQ-5D, were not collected in studies for eladocagene exuparvovec, in part due to the challenges of collecting data in a very severely affected and young patient population of patients who are unable to communicate.
- In the absence of quality of life data from the clinical trials for eladocagene exuparvovec, a vignette study was conducted to determine the quality of life in AADC deficiency.
  - A vignette is a short description about a hypothetical person.
  - In this AADC deficiency vignette study, vignettes were developed based on the following health states: no motor function (worst health state), full head control, sitting unsupported, standing with support, walking with assistance (best health state).
  - Each vignette also described other symptoms of AADC deficiency and it was assumed that the severity of each symptom improved with improving motor function.
  - Members of the UK general population were asked to judge scenarios in which they could live with fewer years of perfect health or more years in one of the health state vignettes (e.g. how many years in perfect health is equivalent to 10 years in the walking with assistance health state?) using a well-established utility elicitation technique called time-trade off.
- The AADC deficiency health state quality of life scores derived from the UK time-trade off study are presented in Table 1 below. Utility values can take a value from 0 to 1, where 0 indicates death, and 1 indicates full health. The results show that quality of life improves as patients gain motor milestones.
- Given that eladocagene exuparvovec allows patients to achieve motor milestones and improve other symptoms related to AADC deficiency, patients treated with the gene therapy are expected to have improved quality of life compared to no gene therapy.

Table 1: AADC deficiency patient quality of life scores by motor milestone health state[34]

Motor milestone state	Patient utility values derived from UK time-trade off
No-motor function	0.494
Full-head control	0.537
Sitting unassisted	0.631
Standing with support	0.676

Walking with assistance	0.728

Score from 0–1 with 1 equivalent to perfect health

Caregiver quality of life impact of eladocagene exuparvovec:

- AADC deficiency has a major physical, emotional and financial impact on families and caregivers of the patient.[15] Caring for a child with AADC deficiency requires around the clock, one-to-one support with all aspects of daily living[16] and has a severe impact on caregiver quality of life.
- Quantitative caregiver quality of life data were not collected in clinical trials for eladocagene exuparvovec or identified in published literature related to AADC deficiency.
- Caregiver disutility was therefore taken from a previous NICE appraisal for a rare disease (mucopolysaccharidosis type IVA; HST 2).[35] These caregiver quality of life values were considered appropriate for AADC deficiency as they provide disutility values for motor milestone health states, and the motor milestone health states aligned with those for AADC deficiency.
- The caregiver disutility values used in HST2[35] (and subsequently in the base case of this submission in AADC deficiency)[35] show that caring for a patient with worse motor function is associated with a more negative impact on caregiver quality of life.
- Given that eladocagene exuparvovec allows patients to achieve motor milestones, caregiver quality of life and the caregiver burden are expected to improve after the patient is treated with eladocagene exuparvovec.

Patient preference information:

- Due to the severe, ultra-rare, and paediatric nature of AADC deficiency, there is no information on patient preference or willingness to accept side effects to receive the benefit of eladocagene exuparvovec.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

- In clinical trials, most side effects were mild and none were considered definitely related to treatment.
- No treatment-related patient deaths were reported across the clinical studies.
- Very common side effects (affect more than 1 in 10 people) that may happen with eladocagene exuparvovec: dyskinesia (involuntary movements), insomnia, and irritability.
- Very common side effects that may happen with the surgery to administer treatment: low levels of red blood cells (anaemia), leakage of the fluid surrounding the brain (possible symptoms include headache, nausea and vomiting, neck pain or stiffness, change in hearing, sense of imbalance, dizziness or vertigo)
- Very common side effects occurring within 2 weeks of the surgery to administer eladocagene exuparvovec, either due to surgery or anaesthesia: gastrointestinal bleeding, diarrhoea, fever, abnormal breath sounds, pneumonia, low level of blood potassium, irritability, hypotension (low blood pressure)
- As eladocagene exuparvovec is a one-off surgical administration, treatment adjustments or discontinuations are not applicable.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:
• Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments. • Please include benefits related to the mode of action, effectiveness, safety and mode of administration
Response: • Eladocagene exuparvovec is the first and only licensed treatment for AADC deficiency and is disease modifying, meaning it treats the underlying cause of the disease. • Currently, patients suffer a life of no motor function and severe symptoms and there is a very high unmet need for disease-modifying treatments. Eladocagene exuparvovec will therefore provide huge clinical benefits to patients by allowing them to develop motor, cognitive, and language skills, and by reducing the occurrence of severe symptoms related to AADC deficiency (e.g. OGC). • Given the improvement in motor function and AADC deficiency symptoms, eladocagene exuparvovec is expected to improve patient survival, quality of life, and daily living. • By improving patient functioning and symptoms, eladocagene exuparvovec will potentially alleviate the substantial caregiver burden of looking after a child with severe AADC deficiency. • Eladocagene exuparvovec is a one-off administration meaning that lengthy and complicated treatment regimens are not required. • Eladocagene exuparvovec is associated with few treatment-related adverse events.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:
• Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments
Response: • Eladocagene exuparvovec is delivered directly to the brain and this procedure may be considered daunting to caregivers of patients with severe AADC deficiency. The pre- and post-operative care may, however, allow patients and caregivers to have more contact time with experienced specialists than without the gene therapy. • While eladocagene exuparvovec offers clear and sustained benefits across a wide range of symptoms associated with AADC deficiency, some patients may continue to require caregiver support and symptomatic treatments.

3i) Value and economic considerations

Introduction for patients:
Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model. In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on: • The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by

patients; were any improvements that would be important to you missed out, not tested or not proven?)

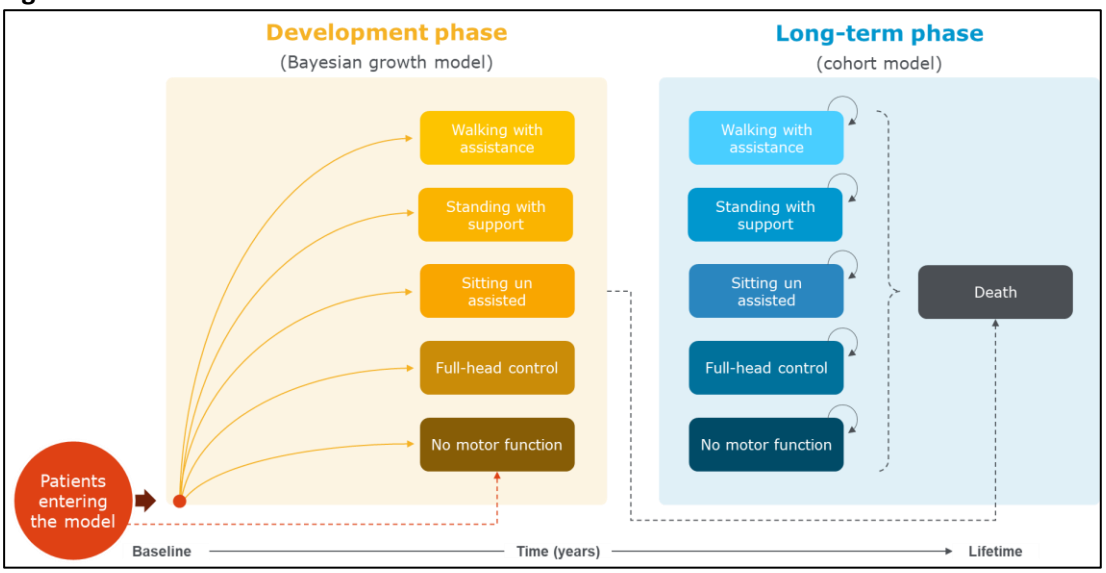
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life

Response:

How the model reflects the condition

- The health economic model compares motor function, quality of life, survival, and costs across the lifetime of patients with severe AADC deficiency treated with eladocagene exuparvovec compared with current best supportive care.
- The model is based on five motor milestone health states (from "worst" to "best"): (i) no-motor function, (ii) full-head control, (iii) sitting unassisted, (iv) standing with support, and (v) walking with assistance. The model assumes that other AADC deficiency symptoms improve as motor milestones improve (as shown in the clinical data and validated by UK experts). Each motor milestone health state is associated with a quality of life score and survival probability.
- All patients with severe AADC deficiency enter the model in the "no-motor function" health state, which is typical of severe patients with AADC deficiency seen in clinical practice (all patients enrolled in the eladocagene exuparvovec clinical trials had no motor functioning at baseline).
- The model includes two phases: (i) a short-term development phase, and (ii) a long-term extrapolation phase.
- In the short-term developmental phase, patients treated with eladocagene exuparvovec or best supportive care are able to improve in motor milestones.
  - Motor milestone achievement with eladocagene exuparvovec is derived from patient-level PDMS-2 scores from clinical trials for eladocagene exuparvovec and extrapolated beyond the clinical trial follow-up period using established statistical models.
  - Motor milestone achievement for best supportive care is derived from a natural history database of all known cases of patients with severe AADC deficiency (i.e. no or poor head control by 2 years of age) described in the literature.[5]
- Once a patient completes the developmental phase, they enter a long-term phase where they remain in the same motor milestone health state for the remainder of their life (Figure 6).
- Each motor milestone health state is associated with a quality of life score, survival duration, and healthcare resource use and costs, with better quality of life, extended survival, and lower costs associated with the higher motor milestone health states.

Figure 6: Cost-effectiveness model structure



Modelling how much a treatment extends life

- Eladocagene exuparvovec is expected to extend life by improving motor function and other AADC deficiency symptoms. The survival improvement of eladocagene exuparvovec in clinical trials is yet to be confirmed due to the need for longer-term data.
- Survival in the economic model is dependent on motor milestone achievement. In the absence of relevant AADC deficiency survival data, proxy (i.e. alternative) motor milestone-related survival estimates were derived from published data in patients with cerebral palsy. Cerebral palsy was identified by global and UK clinical and health economic experts as the most suitable proxy condition.
- Motor milestone achievement in the model is derived from clinical trial data for eladocagene exuparvovec. There are ~5 years of follow-up in most patients and up to 9 years in some patients.
- Beyond the trial follow-up period, the trial data are extrapolated in the economic model using well-established statistical models.

Modelling how much a treatment improves quality of life

- Eladocagene exuparvovec is a one-off surgical administration that provides life-long benefits due to the restoration of AADC enzyme activity.
- A patient's quality of life is expected to improve after eladocagene exuparvovec due to the improved motor function and other symptoms of severe AADC deficiency.
- Quality of life data were not collected in the clinical studies for eladocagene exuparvovec due to the small population size, rarity of the disease and very young age of the patients included.
- To determine quality of life in the economic model, data from the UK time trade off study described in response to question 3f (Table 1) were used. The time trade off study was based on five motor milestone health state vignettes aligned to the motor milestone health states in the model. Each motor milestone health state vignette captures motor function, cognitive function, OGC, as well as other aspects of AADC deficiency, with the underlying assumption that symptoms of AADC deficiency improve as motor function improves. This assumption is supported by trial evidence and UK clinical expert opinion.
- The model also measures the caregiver quality of life impact of looking after a patient with AADC deficiency, with caregiver quality of life improving as patient motor function improves.

- The methods to determine quality of life likely underestimate the quality of life benefits experienced by patients treated with eladocagene exuparvovec given the holistic and life-long improvements in AADC deficiency outcomes following treatment.

Modelling how the costs of treatment differ with the new treatment

- Current best supportive care involves the use of multiple symptomatic treatments and regular annual visits to a wide range of healthcare professionals. The economic model assumes that symptomatic treatment use and healthcare resource use are determined by patient motor function (i.e. more resources are needed in patients with worse motor function).
- In addition to costs associated with current management, patients treated with eladocagene exuparvovec incur a one-off treatment acquisition cost.
- As a highly specialised treatment, eladocagene exuparvovec is associated with administration and monitoring costs before, during, and after the surgery (including additional scans, healthcare visits, hospital stays, etc.). These are all costs and healthcare resources not associated with current management of patients with severe AADC deficiency in the UK.
- The impact of eladocagene exuparvovec on improving patient outcomes is expected to translate into reduced healthcare resource use over time.

Uncertainty

- AADC deficiency is an ultra-rare disease with very limited published data or real-life experience of managing patients compared with more common conditions (e.g. diabetes, cancer, or heart disease).
- Given the above, there are uncertainties in the health economic model. Every effort has been made to reduce the impact of those uncertainties, including discussion and validation of the economic model approach and assumptions with global and UK AADC deficiency clinical experts.
- Key uncertainties include:
    - Using proxy survival data based on cerebral palsy motor milestones instead of data from AADC deficiency. Cerebral palsy was identified as the most appropriate comparator across extensive testing with clinical and health economics experts worldwide. UK experts confirmed it was the most suitable proxy and also confirmed that reliable published survival data for severe AADC deficiency are lacking in the literature.
    - The trials did not capture quality of life and therefore utilities were derived from a UK vignette study using time-trade off elicitation. This is considered by NICE to be a suitable alternative to trial EQ-5D data.

Cost effectiveness results

- Over a patient's lifetime eladocagene exuparvovec is expected to generate a high number of additional quality-adjusted life years (QALYs) compared to best supportive care. One QALY is equivalent to one year of perfect health. This highlights the clear gain in quality of life and survival compared with best supportive care.[36]
- At the list price of eladocagene exuparvovec, the incremental cost-effectiveness of eladocagene exuparvovec versus best supportive care is £176,343 per additional QALY gained. This means that it costs £176,343 for every additional year of perfect health that eladocagene exuparvovec provides versus best supportive care.
- When the agreed discount is applied to the list price of eladocagene exuparvovec, the cost per additional QALY is reduced and eladocagene exuparvovec is cost-effective.

Additional factors

- The health economic model shows that eladocagene exuparvovec offers considerable quality of life and survival gains over best supportive care. The model therefore includes the NICE "QALY modifier", which modifies the incremental cost effectiveness of eladocagene exuparvovec based on the substantial and lifetime expected benefits that it is expected to offer to patients with AADC deficiency.
- The economic model does not capture the high unmet need in severe AADC deficiency and that eladocagene exuparvovec is expected to be the first and only disease-modifying option for patients with severe AADC deficiency. Without gene therapy, patients with severe AADC deficiency are bedbound with no motor function for their entire lifetime and usually die before adolescence.
- Eladocagene exuparvovec is the only hope that patients and caregivers have of meaningful improvements in outcomes, survival, and quality of life.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

- There are currently no licensed treatments, including disease-modifying treatments, for patients with severe AADC deficiency.[4]
- Eladocagene exuparvovec is highly innovative and is the only licensed disease-modifying treatment for severe AADC deficiency. It is also the only licensed therapy that addresses the underlying cause of AADC deficiency. Eladocagene exuparvovec therefore represents a "step change" for patients with severe AADC deficiency and their families.
- Eladocagene exuparvovec is expected to lead to life-changing and transformative benefits to patients and their family caregivers. These benefits are not easily captured in the economic model. Eladocagene exuparvovec is the only hope that patients and caregivers have of meaningful improvements in outcomes, survival, and quality of life.
- Eladocagene exuparvovec also helps advance the understanding and experience of using gene therapies in the treatment of severe and rare genetic disorders in UK practice. UK-specific experience with eladocagene exuparvovec will advance understanding of the disease and its optimal management and pave the way for further treatment innovations. This will in turn generate improved outcomes for children with this ultra-rare, severe, and devastating disease.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

- Eladocagene exuparvovec should be made available to all eligible patients in the UK.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: • What is AADC deficiency? Available here: https://www.ptcbio.com/our-science/therapeutic-areas/about-aadc-deficiency/ • About AADC deficiency. Available here: https://aboutaadc.com/ • AADC deficiency News. Available here: https://aadcnews.com/ • The Journey of Beautiful Destinations. Available here: https://aadcnews.com/the-journey-of-beautiful-destinations-richard-e-poulin-iii/ • AADC deficiency. Available here: https://rarediseases.org/rare-diseases/aromatic-l-amino-acid-decarboxylase-deficiency/ • Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Available here: https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00576-1 Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

- **AIMS**: Alberta Infant Motor Scale, a tool to measure infant development
- **Anticholinergics**: Used to stop involuntary muscle movements in the limbs, lungs, digestive system, urinary tract, and other areas of the body.
- **Aspiration**: When something enters your airways/lungs by accident.
- **Benzodiazepine:** A type of sedative medication to help with insomnia and anxiety.
- **CDITT**: The Comprehensive Developmental Inventory for Infants and Toddlers is a paediatric norm-referenced assessment commonly used for clinical diagnosis of developmental delays in five developmental areas: cognition, language, motor, social, and self-care skills.
- **CPAP**: continuous positive airway pressure is a type of positive airway pressure, where the air flow is introduced into the airways to maintain a continuous pressure to constantly stent the airways open, in people who are breathing spontaneously.
- **CSF neurotransmitter metabolite panels**: cerebral spinal fluid neurotransmitter metabolite panels are useful in diagnosing paediatric neurotransmitter diseases affecting dopamine and serotonin metabolism in the brain and involve a lumbar puncture.
- **Disease-modifying treatment:** A treatment that has a positive impact on the disease course (e.g. by slowing progression).
- **Disutility:** Disutility represents the decrement in utility (valued quality of life) due to a particular symptom or complication. Disutility values are often expressed as a negative value, to represent the impact of the symptom or disease.
- **Dopamine**: dopamine is a neurotransmitter that affects mood, movement, memory and focus.
- **Dopamine agonists:** mimic the action of dopamine.
- **Dystonia**: a movement disorder in which your muscles contract involuntarily, causing repetitive or twisting movements
- **EQ-5D:** EuroQol-5 Dimensions is a tool to measure the quality of life of a person, based on their response to questions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- **Hypoxia**: a condition leading to having low oxygen levels in your tissues
- **Hypotonia:** floppiness caused by decreased muscle tone
- **ICER:** The incremental cost-effectiveness ratio is calculated by dividing the difference in total costs by the difference in health outcomes for an intervention (e.g. eladocagene exuparvovec) versus a comparator (e.g. best supportive care). It provides a value of the extra cost per unit of the health effect.
- **MAO:** Monoamine oxidase inhibitors are antidepressants that prevent breakdown of neurotransmitters like dopamine.
- **OGC**: Oculogyric crisis refers to life-threatening seizure-like spasms of extraocular muscles leading to eye deviation
- **Open label study**: A type of study in which both the health providers and the patients are aware of the drug or treatment being given
- **Plasma enzyme assay**: the assay of enzymes in body fluids, usually blood, that can be used diagnostically or to monitor a clinical condition
- **PDMS-2**: Peabody Developmental Motor Scales Second Edition scale is a questionnaire composed of six subtests that measure interrelated motor abilities of children from birth to 5 years of age. It is validated as a tool to measure motor function in AADC deficiency.
- **Pneumonia**: is swelling (inflammation) of the lungs
- **Proxy:** a variable that is used in place of another
- **QALY:** The quality-adjusted life year is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health.

- **Time-trade off:** A method to determine quality of life. A person will rate the number of years of full health they think is equal to a given number of years in a certain health state.
- **Utility:** the measure of the preference or value that an induvial or society gives a particular health state.[36]
- **Vignette study:** Vignettes are short descriptions about a hypothetical person, presented to participants during research. In the AADC deficiency vignette study, vignettes were developed based on patient motor milestones and other AADC deficiency symptoms.
- **Vitamin B6:** also known as pyridoxine, is required to utilize energy from food, produce red blood cells, and support nerve function.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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7. Brun L, Ngu LH, Keng WT, Ch'ng GS, Choy YS, Hwu WL, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology. 2010 Jul 6;75(1):64–71.
8. Hwu WL, Muramatsu S ichi, Tseng SH, Tzen KY, Lee NC, Chien YH, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency. Sci Transl Med. 2012 May 16;4(134):134ra61.
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10. Hwu WL, Chien YH, Lee NC, Li MH. Natural History of Aromatic l-Amino Acid Decarboxylase Deficiency in Taiwan. In: Morava E, Baumgartner M, Patterson M, Rahman S, Zschocke J, Peters V, editors. JIMD Reports, Volume 40 [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017 [cited 2021 Jul 9]. p. 1–6. (JIMD Reports; vol. 40). Available from: http://link.springer.com/10.1007/8904_2017_54
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12. Chien YH, Lee NC, Tseng SH, Tai CH, Muramatsu S ichi, Byrne BJ, et al. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. Lancet Child Adolesc Health. 2017 Dec 1;1(4):265–73.
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15. Skrobanski H, Williams K, Werner C, O'Neill S, Buesch K, Acaster S. Caregivers research abstract submission: A qualitative study on the impact of caring for an individual with aromatic l-amino acid decarboxylase deficiency (AADCd) [Internet]. ISPOR US 2021. 2021 [cited 2021 Jul 9]. Available from: https://www.ispor.org/heor-resources/presentations-database/presentation/intl2021-3340/110561
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
ID3791_Eladocagene exuparvovec EAG questions_Company responses_24Jun2022_FINAL_CICredacted	1.0	Yes	24 June 2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

Population expected to be treated with eladocagene exuparvovec

A1. Priority question: Please clarify why the wording of the comparator in the company's decision problem in company submission, Section B.1.1, Table 1, ("Best supportive care without eladocagene") differs to that in the NICE final scope ("Established clinical management without eladocagene"). Do "established clinical management" and "best supportive care" differ from each other in the types of treatment, support and care patients receive?

Company response:

"Established clinical management" and "best supportive care" do not differ from each other in the types of treatment, support, and care that patients with aromatic L-amino acid decarboxylase (AADC) deficiency receive. The wording was changed for ease of terminology and to ensure consistency in terminology across various elements of the submission.

A2. Priority question: Company submission, Section B.1.3.1, states that there are "currently 9 known patient(s) in the UK with AADC deficiency" and

company submission, Section B.3.16, states that clinical experts estimate that [redacted] is currently eligible for eladocagene exuparvovec in England and Wales. Please clarify why the other known UK patients would not be eligible for eladocagene exuparvovec, if the reasons are available.

Company response:

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. Of the 9 known patients with AADC deficiency in the UK, [redacted] have already received an experimental gene replacement therapy that restores AADC enzyme functioning and are therefore ineligible for eladocagene exuparvovec, and [redacted] have a mild phenotype that is not aligned to the eladocagene exuparvovec study populations. [redacted] therefore currently eligible for eladocagene exuparvovec in the United Kingdom (UK).

A3. The search strategies reported in company submission Tables 85-89 have a search date of 11 November 2021, whereas the search strategies in company submission Tables 108-112, 115-119, and 123-127 are exactly the same with the same number of reported hits yet have a search date of 23 February 2022. Please can you confirm which dates for the strategies are correct.

Company response:

All searches were originally run on 11 November 2021 and then re-run on 23 February 2022 to ensure searches were conducted within 6 months of the NICE submission deadline (as per NICE guidance). The number of reported hits and all systematic literature review information throughout the submission reflects the results of both the original and re-run searches. All tables included in the company submission should be dated 23 February 2022 (including Tables 85–89, which were erroneously dated 11 November 2021 in the original submission).

A4. The reference provided for the Quality of Life search filter (company submission Section D.1.1.1) does not report the search filter used in the submission, nor do the search strings in the full publication of that reference

match the search filter in the submission. Please confirm whether a published QoL/HSUV filter was used, and if so please provide the reference.

Company response:

The quality of life search filter was directly adapted from Figure 1 of a published poster presentation by Arber *et al.,* titled: "Sensitivity of a search filter designed to identify studies reporting health state utility values".[1] The search string from the Arber *et al.,* presentation was created for MEDLINE searches, so the search string syntax was adapted to embase.com searches for the company submission.

The company also added "OR (caregiver OR carer)" terms to the end of the search string to broaden the searches. The rationale for broadening the searches was to ensure all potentially relevant studies were captured given the rarity of AADC deficiency and limited literature on quality of life.

A5. Please confirm how many reviewers were involved in the quality assessment of the included eladocagene exuparvovec studies, and their roles.

Company response:

As per the NICE guidelines on reviewing research evidence[2], the quality assessment of the included eladocagene exuparvovec studies was completed by one reviewer and a second reviewer had the role of checking for accuracy and consistency. Discrepancies were resolved through discussion between the two reviewers.

Eladocagene exuparvovec studies' inclusion criteria

A6. Please clarify why the minimum age inclusion criteria for all three trials is stated in the company submission (for example, company submission Tables 5, 6 and 7) and in the clinical study reports (CSRs) as ≥ 2 years, yet baseline data in the CSRs show that younger patients were included. For example, study AADC-010 includes a participant aged 21 months, and AADC-011 a participant aged 19 months.

Company response:

In the AADC-010 and AADC-011 studies patients under the age of 2 years were allowed to participate if they had a head circumference big enough for surgery. Study AADC-CU/1601 did not allow patients under 2 years. The inclusion criteria related to minimum age in each study are stated below:

- **AADC-010:** patients aged ≥2 years or head circumference big enough for surgery (please see Row 2, Bullet 2 of Table 6 in the original submission).
- **AADC-011:** patients aged ≥2 years or head circumference big enough for surgery (please see Row 2, Bullet 2 of Table 7 in the original submission).
- **AADC-CU/1601:** patients aged ≥2 years (please see Row 2, Bullet 2 of Table 8 in the original submission).

A7. Inclusion criteria for study AADC-011 is different to the other two studies in that there is an age limit (company submission Table 10 "Not older than 6 years old (72 months) prior to being treated with the study drug."). Please clarify why this age limit was applied?

Company response:

The upper age limit was selected to target eladocagene exuparvovec to the patients who could potentially benefit the most from the treatment. Younger patients may benefit more as they are at an earlier stage of normal development than older patients.

As part of the European Medicine Agency (EMA) regulatory assessment,[3] the Company provided subgroup data on acquisition of key motor milestones by age. The results demonstrated that eladocagene exuparvovec delivers clinically meaningful improvements that were independent of age.[3]

Eladocagene exuparvovec studies' outcomes

A8. Priority question: Please confirm how the Peabody Developmental Motor Scale (PDMS-2) total score (which can range from 0 to 250) should be interpreted. What score ranges indicate no motor function?

Company response:

The PDMS-2 is a developmental motor scale that is divided into 6 subscales:

- Reflexes (8 items),
- Stationary (30 items),
- Locomotion (89 items),
- Object manipulation (24 items),
- Grasping (26 items),
- Visual motor integration (72 items).

For each item in a subscale, a trained assessor assigns a score of ‘0’ (skill not met), ‘1’ (emerging), or ‘2’ (mastery). As there are 249 items, the maximum possible score is 498 (i.e. a score of 2 on all items). A higher PDMS-2 score indicates better motor function. Higher scores in the Stationary, Locomotion, and Object Manipulation subscales indicate stronger gross motor function, whereas higher scores in the Grasping and Visual Motor Integration subscales indicate stronger fine motor function.

For the purposes of the Company submission, “no motor function” is defined as having achieved no key motor milestones. Key motor milestones were scored in the eladocagene exuparvovec studies using the following items:

- Full head control: Item 10 of Stationary subscale,
- Sitting unassisted: Item 14 Stationary subscale,
- Standing with support: Item 28 of the Locomotion subscale,
- Walking with assistance: Item 34 of the Locomotion subscale.

For the primary endpoint, a score of 2 (mastery) on the specific PDMS-2 item was needed for that motor milestone to be attained. A patient was considered as having achieved no motor milestones (i.e. no motor function) if they had a score of 0 or 1 on all of the items described above. All patients in the eladocagene exuparvovec trials had a score of 0 at baseline in all of the items described above and therefore had no motor function at baseline. Similarly, patients in the NHDB were those who had not achieved full head control by 2 years of age.

While higher PDMS-2 scores indicate better motor function, the total possible score can vary from patient-to-patient and at the timepoint of the assessment for a given patient. This is because items are achieved sequentially within each subscale, meaning that a patient must achieve a motor skill before achieving the subsequent skill on the scale. If a patient scores a zero on three consecutive items in a subscale,

the assessor may move on to the next subscale without assessing the remaining items. While the exact level of motor development cannot be determined by the total score because the subscale scores that contribute to the total score can vary, the predicted maximum scores for specific ages for healthy children are shown below, as reported in Table C1 of Folio and Fewell (2000).[4]

- 3 years old (36 Months): total score is predicted to be up to 383 based on the following possible subscale scores:
    - Reflexes (16),
    - Stationary (42),
    - Locomotion (137-138),
    - Object manipulation (30),
    - Grasping (44),
    - Visual Motor integration (113).
- 5 years old (60 months), total score is predicted to be up to 466 based on the following possible subscale scores:
    - Reflexes (12),
    - Stationary (54),
    - Locomotion (170),
    - Object manipulation (44),
    - Grasping (50),
    - Visual Motor integration (136).
- >71 months (PDMS-2 Max), total score is predicted to be up to 483 based on the following possible subscale scores:
    - Reflexes (12),
    - Stationary (>58),
    - Locomotion (>175),
    - Object manipulation (>46),
    - Grasping (52),
    - Visual Motor integration (>140).

A9. Please confirm the aspects of motor function that are included in the PDMS-2 total score presented in the company submission. Does the total score include participants' scores on all six PDMS-2 subtests (reflexes,

stationary, locomotion, object manipulation, grasping and visual-motor integration)?

Company response:
The total PDMS-2 score is typically measured as a sum of all the scores in the six PDMS-2 subtests. However, due to the nature of patients with AADC deficiency, the "reflexes" subscale was not assessed in the eladocagene exuparvovec clinical trials. All other subscales were assessed and contribute to the total PDMS-2 score as seen in the company submission.

As stated in response to question A8, it should be noted that the maximum possible PDMS-2 total score can vary depending on the patient age and their achievement of items in each subscale. In the PDMS-2, items are achieved sequentially within each subscale, meaning that a patient must achieve a motor skill before achieving the subsequent skill on the scale. If a patient scores a zero on three consecutive items in a subscale, the assessor may move on to the next subscale without assessing the remaining items.

It should also be noted that PDMS-2 total score was not used in the economic model. The economic model uses the key motor milestone attainment, which was measured in the eladocagene exuparvovec trials as described in response to Question A8.

A10. Company submission, section B.2.2, Table 5, suggests to us that only 'mastery' of motor milestones was assessed in study AADC-CU/1601, while in studies AADC-010 and AADC-011 participants' achievement of motor milestones was assessed as either 'newly emerging' or 'mastery'. Is our interpretation of the information in the table about the assessment of the primary outcomes correct?

Company response:
As stated in response to question A8, each item in the PDMS-2 scale is scored with either a 0 (skill not met), 1 (emerging), or 2 (mastery). The primary endpoint in all eladocagene exuparvovec trials was key motor milestone achievement, as determined based on a score of 2 (mastery) for the following items:

- Full head control: Item 10 of Stationary subscale,

- Sitting unassisted: Item 14 Stationary subscale,
- Standing with support: Item 28 of the Locomotion subscale,
- Walking with assistance: Item 34 of the Locomotion subscale.

The Company evidence submission also includes data on “emerging” or “mastery” of the items above, for AADC-010 (Table 15) and AADC-011 (Table 20). The EAG is correct that a corresponding table was not provided in the Company submission for the AADC-CU/1601 study. For completeness and consistency, we have therefore provided tables below for the cumulative (Table 1) and new (Table 2) achievement of “emerging” or “mastery” of the items described above, for AADC-1601. In addition, we have provided the corresponding tables for the pooled population (Table 3 and Table 4).

Table 1: AADC-1601: Cumulative motor milestone achievement (emerging or mastery) by time point following eladocagene exuparvovec treatment (ITT population, N=8)

Milestone (Emerging or Mastery)	Number of subjects assessed by timepoint, n/N (%)									
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 24	Month 36	Month 48	Month 60	Month 60+
Head control	0/8	[redacted]								
Sitting unassisted	0/8	[redacted]								
Standing with support	0/8	[redacted]								
Walking with assistance	0/8	[redacted]								

Abbreviations: PDMS-2 - Peabody developmental motor scale, second edition
The number of subjects assessed at each timepoint is shown.
Assessed = PDMS-2 scores of 0,1 or 2; emerging and mastery = PDMS-2 scores of 1 or 2
Source: Clinical study report for AADC-1601 (N=8) and Table.CUM.MM for NTUH-AADC-1601

Table 2: AADC-1601: New motor milestones achievement (emerging and mastery) by time point following eladocagene exuparvovec treatment

Milestone (Emerging or Mastery)	Number of subjects assessed by timepoint, n/N (%)										
	BL*	Month 3	Month 6	Month 9	Month 12	Month 24	Month 36	Month 48	Month 60	Month 60+	Overall
Partial head control	[redacted]										
Head control											
Sitting with assistance											
Sitting unassisted											
Crawling											
Standing with support											
Standing without support											
Walking with assistance											
Walking to toy											

Abbreviations: BL – baseline; PDMS-2 - Peabody developmental motor scale, second edition
The number of subjects assessed at each timepoint is shown.
**In AADC-CU/1601 baseline data were not available for 3 patients*
Assessed = PDMS-2 scores of 0,1 or 2; emerging and mastery = PDMS-2 scores of 1 or 2
Source: Clinical study report for AADC-1601 (N=8) and T.NEW.MM for NTUH-AADC-1601

Table 3: Pooled: Cumulative motor milestone achievement (emerging and mastery) by time point following eladocagene exuparvovec treatment (ITT population, N=28)

Milestone (Emerging or Mastery)	Number of subjects assessed by timepoint, n/N (%)									
	BL	Month 3	Month 6	Month 9	Month 12	Month 24	Month 36	Month 48	Month 60	Month 60+
Head control	0/28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting unassisted	0/28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support	0/28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with assistance	0/28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL – baseline; PDMS-2 - Peabody developmental motor scale, second edition
The number of subjects assessed at each timepoint is shown.
Assessed = PDMS-2 scores of 0,1 or 2; emerging and mastery = PDMS-2 scores of 1 or 2
Source: Table.CUM.MM for NTUH-AADC-010, NTUH-AADC-011 and NTUH-AADC-1601 (N=28)

Table 4: Pooled: New motor milestone achievement (emerging and mastery) by time point following eladocagene exuparvovec treatment

Milestone (Emerging or Mastery)	Number of subjects assessed by timepoint, n/N (%)										
	BL*	Month 3	Month 6	Month 9	Month 12	Month 24	Month 36	Month 48	Month 60	Month 60+	Overall
Partial head control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Head control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting unassisted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing without support	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking to toy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL – baseline; PDMS-2 - Peabody developmental motor scale, second edition
The number of subjects assessed at each timepoint is shown.
**In AADC-CU/1601 baseline data were not available for 3 patients*
Assessed = PDMS-2 scores of 0,1 or 2; emerging and mastery = PDMS-2 scores of 1 or 2
Source: Table.NEW.MM for NTUH-AADC-010, NTUH-AADC-011 and NTUH-AADC-1601 (N=28)

A11. Company submission, section B.2.2, Table 5, suggests that full head control was measured using item #10 of the PDMS-2 Stationary subscale,

sitting unassisted was measured using item #14 of the Stationary subscale, standing with support was measured using item #28 of the Locomotion subscale and walking with assistance was measured using item #34 of the Locomotion subscale in all three eladocagene exuparvovec studies. Is our interpretation correct?

Company response:
The Company can confirm that the EAG's interpretation is correct.

A12. Priority question: Please clarify whether the achievement of motor milestones results for study AADC-011 presented in company submission, section B.2.6.2, Table 19, are for the number and proportion of participants who achieved a) 'mastery' only of these motor functions or b) either 'newly emerging' or 'mastery' scores.

Company response:
The Company confirms that option (a) is correct. In B.2.6.2, Table 19 of the company submission, the results for key motor milestone achievement in AADC-011 are for "mastery" of motor milestones only. Results for "newly emerging" or "mastery" scores for the AADC-011 trial were presented in Table 20.

A13. Company submission, section B.2.5, states that the AADC-CU/1601 study was a retrospective observational study. Please clarify how outcome data were obtained retrospectively in this study (for example, via participants' medical records).

Company response:
AADC-CU/1601 was a retrospective observational study that abstracted data from the medical records of 8 patients who received eladocagene exuparvovec in a compassionate use interventional study.

Between February 2010 and December 2011, 8 patients received eladocagene exuparvovec in a compassionate use study (AADC-CU). The observational AADC-CU/1601 study was subsequently designed and executed to formally collect data from the compassionate use study. Each of the 8 patients enrolled in the compassionate use study were enrolled in the AADC-CU/1601 observational study and data were

collected using a case report form designed to capture per-patient clinical data from a range of sources.

In the compassionate use study, a schedule of assessments was prospectively defined. The AADC-1601 protocol allowed for the collection of the data from each AADC-CU study patient's medical record and for the prospective collection for a period of up to 60 months following eladocagene exuparvovec infusion. Sources of data were patients' medical charts, laboratory reports, and imaging studies (see Table 1 and Table 2 in the AADC-CU/1601 CSR). Data collected were transcribed onto case report forms.

A14. Please confirm whether or not patients' health-related quality of life (HRQoL) (i.e. the HRQoL of the children with AADC deficiency) was measured in studies AADC-010, AADC-011 and AADC-CU/1601. If HRQoL was assessed, please provide details of the measure(s) used and the results.

Company response:
Patient HRQoL was not measured in studies AADC-010, AADC-011, or AADC-CU/1601 given that patients in the studies were unable to communicate effectively due to being very young and having severe cognitive and language impairment.

A15. The company submission Executive Summary states that the World Health Organisation-BREF survey was used to retrospectively measure caregiver quality of life. We note results are available in Tai et al. (2022) (company submission reference number 10). Please clarify if any other measures of caregiver quality of life was used in studies AADC-010, AADC-011 and AADC-CU/1601. If any other measure(s) was used, please provide details of the measure(s) and the results.

Company response:
Caregiver health-related quality of life was not prospectively measured in studies AADC-010, AADC-011, or AADC-CU/1601.

As detailed in Tai *et al.* (2022)[5], the WHO-BREF questionnaire was retrospectively completed by 17 caregivers of patients who received eladocagene exuparvovec. All data collected from the questionnaire are reported in Tai *et al.* (2022).

No further caregiver quality of life data were collected from caregivers of patients in the AADC-010, AADC-011, or AADC-CU/1601 studies.

A16. In the AADC-010 and AADC-011 studies, were all outcome assessors trained in using the Peabody Developmental Motor Scales - Second Edition, Alberta Infant Motor Scale, and the Bayley Scale of Infant Development - Third Edition? In study AADC-1601 were all assessors trained in using the Peabody Developmental Motor Scales - Second Edition, Alberta Infant Motor Scale (AIMS), and the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT)?

Company response:
All outcome assessors in AADC-010, AADC-011, and AADC-1601 were trained in using the respective instruments.

- In AADC-010: a single qualified examiner administered PDMS-2, AIMS and Bayley-III.
- In AADC-011: a single qualified examiner administered PDMS-2 and Bayley-III, and two qualified examiners were used for measurement of AIMS.
- In AADC-CU/1601: two qualified examiners administered PDMS-2, AIMS and CDIIT.

The examiner used in Study 010 and 011 was 1 of the 2 examiners for Study 1601. For all 3 studies, the same subject was evaluated by the same examiner for the entire study.

A17. From the company submission and from the CSRs, it is unclear what constitutes the outcome of "autonomic nervous system functioning" specified in the NICE final scope and decision problem. Please clarify what outcome(s) constitutes "autonomic nervous system functioning".

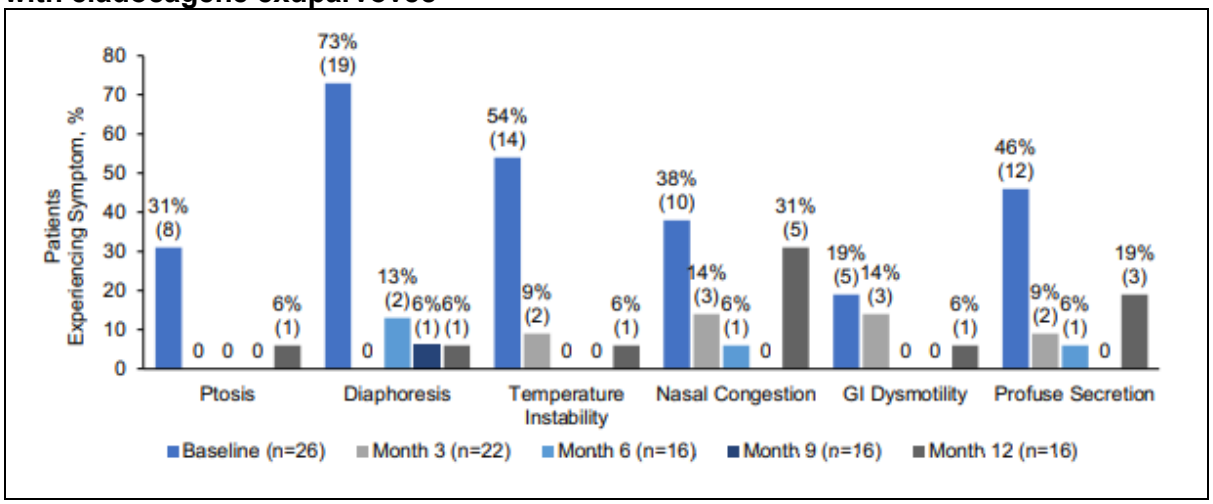
Company response:
Symptoms associated with autonomic nervous system (ANS) dysfunction observed in patients with AADC deficiency include ptosis (drooping eyelid), miosis (constricted pupils), nasal congestion, excessive drooling, stridor (noisy breathing), diaphoresis

(excessive sweating), temperature instability, hypotension (low blood pressure), bradycardia (slow heart rate), heart rhythm abnormalities, gastrointestinal (GI) dysmotility, diarrhoea, and obstipation (severe form of constipation).[6]

ANS functioning was analysed in post-hoc examinations in the first year following treatment with eladocagene exuparvovec for the three trials (AADC-010, AADC-011, and AADC-CU/1601). It should be noted that data were only collected for patients who experienced ANS symptoms at baseline, as opposed to the full cohort of patients. Furthermore, data were not available at every timepoint for the entire eligible cohort, meaning an incomplete set of results was gathered.

The proportion of patients experiencing ANS symptoms (including ptosis, diaphoresis, temperature instability, nasal congestion, GI dysmotility, and profuse secretion) reduced in all assessed categories from baseline to Month 12, with considerable improvements observed as early as the first post-treatment screening at Month 3 (Figure 1). From baseline to Month 12, there was a 7–67% reduction in the proportion of patients experiencing each symptom, highlighting the benefit of eladocagene exuparvovec for ANS functioning (Figure 1).[7]

Figure 1: Percentage of patients experiencing autonomic symptoms after treatment with eladocagene exuparvovec



Abbreviations: GI – gastrointestinal
The number of subjects assessed at each timepoint is shown.
Source: Hwu et al., 2022. Early Clinical Improvements Following Treatment With Eladocagene Exuparvovec in Patients With Aromatic L-Amino Acid Decarboxylase Deficiency. Poster presented at ISPMD 2022.[7]

Eladocagene exuparvovec studies' results

A18. For all three studies, please confirm the schedule of assessment for adverse events, as currently this is unclear (for example, how frequently were adverse events assessed?).

Company response:

The schedule of assessments for adverse events in each study was as follows:

- **AADC-010:** As per the protocol, adverse events (AEs) were monitored from dosing day through the end of the study and serious adverse events (SAEs) were monitored from screening through to the end of the study. AEs were assessed within 7 days of the following timepoints post-surgery: Day 1, Month 3, Month 6, Month 9, Month 12. Please see the AADC-010 protocol[8] for more information.

- **AADC-011:** As per the protocol, AEs were monitored immediately after signing the informed consent form through to 1 year after the surgical procedure. AEs were assessed at the screening visit at 3 months prior to dosing and during the baseline examination from Day 28 to Day 1 pre-surgery. AEs were also monitored on the day of the surgery. Following treatment, AEs and SAEs were recorded at scheduled visits to the investigational site within 7 days of the following post-surgery timepoints: Day 7, Month 3, Month 6, Month 9, Month 12, Month 13. At the Month 12 follow-up, patients were asked if they consented to participate in a long-term follow-up program including AE monitoring. For more information, please see the AADC-011 Protocol v5.0[9].

- **AADC-1601:** AEs and SAEs were recorded throughout the study at scheduled visits to the investigational site at the following timepoints: on the day of the surgery, Days 3-7, every 1 month from Month 1 to Month 12, every 6 months (±3 month) from Month 12 to Month 60. Please see the AADC-CU/1601 protocol[10] for more information.

A19. For study AACD-011, please provide all the tables that are listed in the CSR under the following headings:

a) **14.2. Efficacy Data Summary Figures and Tables**

Company response:
Please refer to the AADC-011 tables and figures in the reference pack supplied by the Company alongside this response document.

b) **14.3. Safety Data Summary Figures and Tables**

Company response:
Please refer to the AADC-011 tables and figures in the reference pack supplied by the Company alongside this response document.

A20. For study AACD-1601, please provide all figures, tables and supplemental tables and figures in the CSR listed under the heading "14 TABLES, FIGURES, AND GRAPHS".

Company response:
Please refer to the AADC-1601 CSR[11] in the reference pack supplied by the company alongside this response document.

A21. Priority question: The company submission Executive Summary states that the AADC-CU/1601 study found that "Patients with 5-10 years of follow-up continue to show improved motor function compared with baseline" and references company submission reference 10 (Tai et al., 2022). Please confirm whether or not any other longer-term follow-up data are available for any measured outcome for any participants included in the AADC-010 and AADC-CU/1601 studies beyond five years and the AADC-011 study beyond 12 months. If data are available, please provide a brief summary of the results.

Company response:
Longer-term follow-up data are available for some patients for key motor milestone achievement, as assessed using PDMS-2 scores. The length of follow-up data supporting eladocagene exuparvovec is extremely valuable and a strength of the Company submission given the difficulties in collecting data for rare diseases. The

data presented below are for a January 2022 data cut-off. The long-term data further supports the durable treatment effect with eladocagene exuparvovec, which was also concluded by the EMA during their regulatory review.[3]

In AADC-010:

- [redacted] patients had data beyond the 60-month trial follow-up duration. The longest follow-up time point was 72 months for [redacted] patients, and 84 months for [redacted] patient.
- Of the [redacted] patients with follow-up beyond 60 months, [redacted] patients maintained their highest motor milestone at their last follow-up time point.
- One patient could sit unassisted at their Month 60 visit. Between the patient's Month 60 and Month 72 assessments, the patient had surgery for hip dysplasia and was therefore not able to sit unassisted at the Month 72 or Month 80 visit. The patient experienced an improvement in motor function from Month 72 to Month 80, indicating a recovery from surgery.

In AADC-011:

- [redacted] patients had data beyond the 12-month trial follow-up duration. The longest follow-up time point was 30 months for [redacted] patients, 48 months for [redacted] patient, and 60 months for [redacted] patients.
- Of the [redacted] patients with follow-up beyond 12 months, [redacted] improved their motor milestone attainment and [redacted] maintained their motor milestone attainment compared to the 12-month time point.
- The [redacted] patients who had "full head control" at Month 12 could "stand with support" or better (walk with assistance) at their last follow-up time point.
- Of the [redacted] patients who had no motor milestone achievement at Month 12, [redacted] achieved walking with assistance and [redacted] achieved sitting unassisted at the time of their last follow-up.

- The patient with the highest motor milestone achievement at Month 12 (sitting unassisted) achieved standing with support by their last follow-up time point (Month 48).

In AADC-CU/1601:

- [redacted] patients had data beyond the 60-month trial follow-up duration. The longest follow-up time point was 72 months for [redacted] patient, and 120 months for [redacted] patients.

- Of the [redacted] patients with follow-up beyond 60 months, [redacted] patients maintained their highest motor milestone at their last follow-up time point, with [redacted] patient maintaining an emerging attainment of their highest milestone.

ITC feasibility assessment and Natural History Database

A22. Priority question: Please summarise evidence on the factors that are prognostic of motor function development AADC deficiency.

Company response:

To determine appropriate prognostic factors for motor function in AADC deficiency, the Company consulted with clinical experts across advisory boards and individual interviews. Generally, experts gave varying responses when discussing both prognostic variables and adjustment factors due to the uncertainty and general lack of published evidence on prognostic factors in AADC deficiency.

In an advisory board conducted in July 2021,[12] clinical experts in AADC deficiency stated that age, motor milestone achievement, and non-motor symptoms (e.g. oculogyric crisis, dystonic disorders, pulmonary infection) should be considered as adjustment covariates in an indirect treatment comparison. In a separate set of clinician interviews, age, sex, weight, severity of disease, frequency of oculogyric crises, autonomic instability and cognitive function were mentioned as important prognostic factors. Of these factors, only motor milestone achievement and patient sex was reported regularly in the publications utilised in the natural history database (NHDB).

While age and non-motor symptoms were considered by experts to be prognostic factors for motor function, neither were reported routinely in the publications contributing to the NHDB. It was not possible, therefore, to include patient age and non-motor symptoms as adjustment covariates. The publications in the NHDB did, however, report age at diagnosis data, so age of diagnosis was used as a proxy for age. It should be noted that clinical experts did not think that age at diagnosis would be a good criterion for matching as it may be affected by external factors; for example, delayed diagnosis is common for rare diseases such as AADC deficiency.

In addition to matching based on age, as the matching population is the subset of patients who had no motor milestone attainment by age 2, both the presented ITC and naïve analyses are already implicitly matched by motor milestone attainment.

Given the lack of routinely published information in the NHDB for the prognostic factors identified by clinical experts, the only factors that could be considered as adjustment covariates in the ITC feasibility analysis were those which data were available for patients in both the clinical studies and the NHDB and for which the data varied between the population groups. Thus, sex, race and mutation category were the only possible adjustment covariates to consider in the matching analysis.

A23. Priority question: Please extend company submission, Section B.2.9.3, Table 27, to include all the additional data collected as part of the Natural History Database (NHDB) (as noted in company submission, Section B.2.9.1.3); that is, PDMS-2 at baseline, AIMS at baseline, disease severity, treatment given, and any other available data. Please include corresponding data from the eladocagene exuparvovec studies.

Company response:

Please see Table 5 for an update of Company submission Table 27 to include available data for other characteristics in the NHDB (new data in blue text).

As the NHDB is based on a systematic review of cases of AADC deficiency reported in the literature, most of the baseline outcomes requested by the EAG were not routinely reported in the original publications (e.g. PDMS-2, height, weight).

Of the characteristics requested by the EAG in question A23, only information on the AIMS score at baseline is available from the NHDB, and it is only available for 5 patients in the NHDB. The baseline total AIMS score for the 5 patients with data in the NHDB is similar to the baseline total AIMS score of patients in the eladocagene exuparvovec studies.

Information on treatments given to patients is presented as part of the Company response to question A42. Information on the other endpoints is not available in the NHDB and so is not reported in the table below.

Table 5. Patient characteristics across the natural history database and the three eladocagene exuparvovec trials

	Natural history database	Eladocagene exuparvovec trials
N	49	28
Sex		
Female	17 (34.6%)	14 (50.0%)
Male	26 (53.1%)	14 (50.0%)
Unknown	6 (12.2%)	0 (0.0%)
Age at diagnosis mean(sd)	3.4 (3.5)	3.4 (3.5)
Race		
Chinese	22 (44.9%)	16 (57.1%)
Japanese	8 (16.3%)	0 (0.0%)
Other Asian	1 (2.0%)	10 (35.7%)
White	8 (16.3%)	1 (3.6%)
Unknown	10 (20.4%)	1 (3.6%)
Mutation Category		
Heterogeneous	20 (40.8%)	11 (39.3%)
Homogeneous	16 (32.7%)	17 (60.7%)
Unknown	13 (26.5%)	0 (0.0%)
Baseline AIMS score		
Missing data, N (%)	44 (89.8%)	[redacted]
0, N (%)	4 (8.2%)	[redacted]
1, N (%)	1 (2.0%)	[redacted]
2, N (%)	0	[redacted]
3, N (%)	0	[redacted]
4, N (%)	0	[redacted]
≥5, N (%)	0	[redacted]
Mean score	NA	1.60–2.92
Disease severity	No or poor head control by age 2 years.	No or poor head control at baseline.

**AIMS baseline data were not available for 3 patients at baseline in AADC-CU/1601*
Abbreviations: AIMS – Alberta Infant Motor Scale; NA – not applicable; SD – standard deviation

A24. Please clarify why is race missing from the list of data reported to be collected in the NHDB study in company submission Section B.2.9.1.3).

Company response:

The Company thank the EAG for pointing out this discrepancy. Data on race were collected in the NHDB and are reported in Table 27 of the Company submission.

A25. Please summarise the phenotype data in the eladocagene exuparvovec studies and the NHDB populations for the N = 49 and N = 185 populations.

Company response:

Once the adjudication of motor milestones was completed by the clinicians (described in more detail in response to question A26), phenotype definitions were established. Phenotype definitions considered the age of the subject, the history of observations, and motor milestone achievement. Phenotypes were categorised as follows:

- **Severe**: a patient who had no or poor head control by 24 months of age, similar to the eladocagene exuparvovec study populations.
- **Mild**: a patient who could walk with assistance by 24 months of age.
- **Moderate**: a patient with motor milestone assessments but who did not meet the definitions for “severe” or “mild”.
- **Unknown**: a patient whose motor milestone information was not available or insufficient to classify as severe, moderate, or mild.

In the N=185 population, sufficient information was reported for the disease severity to be determined for 96 patients, with the remainder (N=89) having an unknown severity. Disease severity was adjudicated by two clinicians. Of the 96 patients with severity information, 69 were classed as severe (72%; i.e. having a phenotype similar to patients in the eladocagene exuparvovec studies), 23 were classed as moderate (24%), and 4 were classed as mild (4%).

Of the 69 NHDB patients classed as having a similar phenotype to the patients in the eladocagene exuparvovec studies, 20 were classed as PTC patients (i.e. those included in the eladocagene exuparvovec studies and with published data at the time of the December 2019 SLR for the NHDB) and were therefore removed from the NHDB arm in the ITC feasibility assessment and Company submission. The final NHDB

presented in the Company submission (see Sections B.2.9 and B.3.3.1.2) was therefore made up of the N=49 “non-PTC” patients with similar phenotype to patients in the eladocagene exuparvovec studies.

A26. Please clarify if the definition of motor milestones was consistent across the eladocagene studies and the NHDB?

Company response:

The definition of motor milestones was broadly consistent across the NHDB and eladocagene exuparvovec studies.

In the eladocagene exuparvovec studies, PDMS-2 was used to determine motor milestone achievement. The PDMS-2 motor skill items that were used to assess key motor milestones are summarised in Table 6 below**.** Each skill item is assessed as a simple 3-level scoring system, where 0 = the test was attempted and the subject could not perform, 1 = the skill is emerging, and 2 = the subject has mastered the motor skill. For a key motor milestone to be achieved for the primary endpoint in the eladocagene exuparvovec studies, a score of 2 (mastery) was required for the PDMS-2 item.[13]

Table 6: PDMS-2 mapping onto key motor milestone achievement

PDMS-2 motor skill item	Key motor milestone achievement
Stationary item 10	Full head control
Stationary item 14	Sitting unassisted
Locomotion item 28	Standing with support
Locomotion item 34	Walking with assistance

In the NHDB, motor milestone achievement for each patient was determined based on a scoring system of 1–9 (see Column 1 and 2 of Table 7) that was anchored to the PDMS-2 scale (see Column 3 and 4 of Table 7). The scoring system ensured consistency and standardisation of analysis of patients in the NHDB given that patients were identified from a wide range of publications with varying methods and level of detail in the descriptions of their motor function. The scoring system was also anchored to PDMS-2 to ensure alignment with the methods used to determine motor milestone achievement in the clinical studies for eladocagene exuparvovec.

Patient scoring was determined by two clinicians independent to the data entry team. The adjudication was performed by the clinicians on a "per statement" basis, so each individual statement regarding motor function was adjudicated individually, independent from other statements. This made the process agnostic from individual interpretation based on authors, subjects, disease progression, and other potential influencing factors.

Table 7: Summary of scoring for motor milestone acquisition

NHDB scoring number	Analytical term (NHDB motor milestone scoring system)	PDMS-2 item (anchoring term)	PDMS-2 description (anchoring term)	Normal time to achieve from birth
1	Lift head against gravity	Stationary 6	Extending head (held in suspended vertical position, observe for midline alignment)	3 months
2	Lift head and push up	Locomotion 5	Extending trunk (lying on stomach, forearms on surface, observe for elevation of head/upper trunk)	3–4 months
3	Full head control	Stationary 10	Aligning head (sitting, supported with pillows around hips)	6 months
4	Sitting with support	Stationary 11	Sitting (maintain for 8 seconds for score of “2”)	6 months
5	Rolling from side to side, use of core	Locomotion 17	Rolling (rolling from back to stomach)	8 months
6	Sitting	Stationary 14	Sitting (unsupported)	10–11 months
7	Crawling	Locomotion 20	Creeping (hands and knees)	10 months
8	Stepping	Locomotion 28	Stepping (supported)	12 months
9	Walking	Locomotion 34	Walking (supported)	14 months

A27. Priority question: The methodology used for the indirect treatment comparison (ITC) is propensity score matching which requires individual participant data for both eladocagene exuparvovec and comparator studies. Was matching to aggregate data considered using, for example, simulated treatment comparisons or matching-adjusted indirect comparisons? Are there any aggregate data sources for best supportive care which were identified and could have facilitated such analysis? For example, in the systematic review update, 15 studies were identified and many were excluded due to their not providing sufficient “evidence to identify unique patients for data given” (company submission Table 26). Please provide further details of each of these excluded studies, including patient numbers and any rationale as to why they could not have been used for aggregate population matching.

Company response:

As a small note, the Company would like to correct the number of publications identified from the systematic literature review update. Table 26 in the Company submission shows that 16 publications were identified in the Company systematic literature review, of which 2 were already included in the NHDB. In addition, the Company identified an error within this table in which Boehnke *et al.* (2021)[14] was duplicated and appeared twice. Therefore, rather than 15 excluded publications, the correct number of excluded publications is 13.

As mentioned in the NICE DSU, matching-adjusted indirect comparisons (MAICs) are designed to meet a very specific situation in which companies have access to IPD from their own trials, but only aggregate outcomes (as summarised in a publication) from a competitor's trials.[15] As there are patient-level data for both comparators in this appraisal (BSC in the NHDB, and eladocagene exuparvovec in the AADC-010, AADC-011, and AADC-CU/1601 trials), an MAIC was not considered an appropriate ITC methodology.

Similarly, simulated treatment comparison (STC) is another type of population-adjusted ITC mentioned in the NICE DSU TSD 18[15] alongside MAICs. STCs use linear regression models for the relationship between population characteristics and outcomes in a trial where IPD is available, then use the model to estimate that outcome for the other trial population. In this case, because comparator data are available (NHDB), an STC was not considered.

In addition to the above reasons, adjusting on covariates in an MAIC or STC would likely lead to a significantly reduced sample size and given the already small initial sample, the results would not be credible.

Aggregate population matching would not have been appropriate using any of the 13 excluded publications for the reasons detailed in Table 8 below. The evidence base for the NHDB comprises 98 publications including 49 patients where sufficient data were available to determine disease severity and motor milestones. The NHDB is far more substantial than the 13 excluded publications as it comprises the vast majority, if not all, of the high-quality natural history evidence within AADC deficiency, and surpasses the evidence quality available for any one aggregate data source for the best supportive care arm in the Company submission.

The EMA considered the NHDB comparator arm to be appropriate to contextualise the effects of eladocagene exuparvovec as part of the regulatory appraisal process.[3]

Table 8: Reason for excluding studies identified in the February 2022 SLR from aggregate population matching

Comparator	Publication	Rationale for exclusion from ITC	Rationale for exclusion from aggregate population matching	Patient number
hAADC administered in SNc and VTA	Gupta *et al.*, 2020[16]	BSC arm has insufficient evidence* to identify unique patients from data given and thus is not suitable for use in the NHDB.	Details for the BSC arm only given at baseline, so unsuitable for aggregate population matching.	N=7
	Bankiewicz *et al.,* 2019[17]	BSC arm has insufficient evidence* to identify unique patients from data given and thus is not suitable for use in the NHDB.		N=6
	Pearson *et al.,* 2019[18]	BSC arm has insufficient evidence* to identify unique patients from data given and thus is not suitable for use in the NHDB.		N=7
	Pearson *et al.,* 2021[19]	BSC arm consists of only data at baseline and is not suitable for use in the NHDB.		N=7
ATMPs	Boehnke *et al.* 2021[14]	Insufficient data (only qualitative assessment) of motor milestone achievement reported.	Qualitative data reported, unsuitable for aggregate population matching.	NR
BSC/ Natural history	Pearson *et al.*, 2020[20]	Indirect information provided (clinician questionnaires), inferior to case reports utilised in NHDB.	As the questionnaires were completed online and combined with answers from parents are caregivers, the data quality was less reliable and unsuitable for use in aggregate population matching.	N=63
	Saberian *et al.*, 2021[21]	Questionnaire data, inferior to case reports utilised in NHDB.	Data were from a brief abstract, which made it difficult to ascertain the quality of evidence. Therefore, data were deemed unsuitable for use in aggregate population matching.	N=20

Comparator	Publication	Rationale for exclusion from ITC	Rationale for exclusion from aggregate population matching	Patient number
	Williams *et al.*, 2021[22]	Questionnaire data, inferior to case reports utilised in NHDB.	Qualitative data reported, unsuitable for aggregate population matching.	N=13
	Wen *et al.*, 2020[23]	Insufficient follow-up/long-term data for use in NHDB.	A genetic study with only data given at baseline, therefore unsuitable for aggregate population matching.	N=23
	Mastrangelo *et al.*, 2019[24]	Not suitable for NHDB as insufficient evidence* to identify unique patients from data given.	No quantitative measurement of improvement in motor function. unsuitable for aggregate population matching.	N=5
	Saberian S *et al.* 2021[25]	Indirect information provided (clinician questionnaires), inferior to case reports utilised in NHDB.	Data were from a brief abstract which made it difficult to ascertain the quality of evidence. Therefore, data were deemed unsuitable for use in aggregate population marching.	N=20
	Havalı C *et al.* 2021[26]	No information on motor milestone achievement reported.	No information on motor milestone achievement reported.	N=5
	Ling T-K *et al.* 2021[27]	No information on motor milestone achievement reported.	No information on motor milestone achievement reported.	N=8

**Please note that "insufficient evidence to identify unique subjects" was defined based on the criteria used for the NHDB (i.e. little or no demographics and subject detail available or no individual subject information available).*
BSC – Best supportive care; hAADC – Human aromatic L-amino acid decarboxylase; ITC – Indirect treatment comparison; NHDB – Natural History Database; NR – Not reported; sNC – Substantia nigra pars compacta; VTA – Ventral tegmental area

A28. Please elaborate as to why matching on sex alone should be rejected due to distribution of weights (company submission Section B.2.9.5).

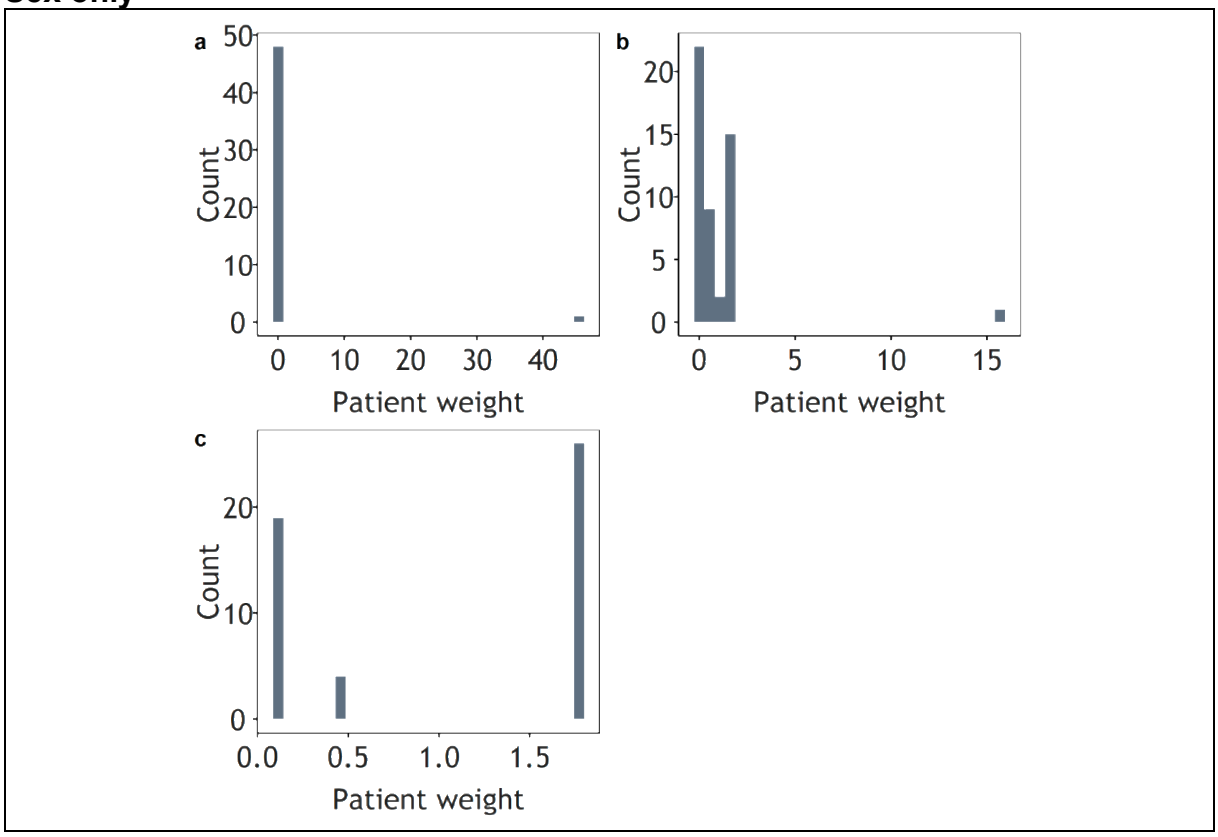
Company response:

As can be seen in Figure 39 in the company submission (also shown in Figure 2 below), weights vary widely between patients when matching on sex alone. A small number of patients therefore carry an excessively large weight in the analysis. Additionally, as can be seen in Table 5 (in the response to A23), data on sex are missing for 12.2% of patients in the NHDB. When data are missing, those patients receive a low weight due to the matching covariate not being available. The high

variability in patient weights makes the analysis unstable and impacts the reliability of the results.

Regardless of the weight distribution, it can be seen from the Company response to A29 that the naïve comparison is a more conservative approach for the Company submission because it produces more optimistic results for the BSC arm than the matched analyses. This is because the only two patients in the NHDB who experienced any improvement in their motor milestones had a very low weight in most of the matched analyses.

Figure 2: Distribution of patient weights after the matching analysis for models (a) Sex, race, age at diagnosis, mutation category; (b) Race and sex; and (c) Sex only



A29. Priority question: Please present the motor milestone results for the propensity score matching exercise. Please report the methods used, e.g. logistic regression or inverse probability weighting, and whether these results were consistent.

Company response:

The Company conducted an approximate matching exercise using propensity score matching methods. This method aims to control for self-selection and extend causal inference into non-randomized studies.[28] Propensity scores are estimated for each patient, which gives the conditional probability of assignment to a particular treatment or control given a set of patient baseline covariates.[28] In this analysis, propensity scores were calculated using logistic regression.

Propensity scores are then used to match treated patients (in this case those patients in the eladocagene exuparvovec studies) to an untreated patient (in this case those patients in the NHDB). The underlying assumption of propensity score matching is that those patients in the NHDB can be compared to those patients in the clinical trials based on a set of baseline characteristics used to estimate the propensity scores.

The motor milestone results for each of the model specifications, including those requested as part of question A30 (i.e. “sex and mutation category” and “mutation category alone”), are presented in Table 9. For all of the specifications, the naïve analysis is more conservative than the matched analyses as it estimates that a higher proportion of patients in the BSC arm progress out of the “no motor milestone” health state.

The propensity score analysis results should be interpreted with caution. The effective sample size and the distribution of patient weights for each model specification indicates uncertainty and a considerable loss of information when matching, essentially rendering any results from these analyses meaningless (this is further detailed in the company submission in section B.2.9).

Table 9: Distribution of patients across motor milestone health states in the BSC arm based on different matching covariates

	No motor milestone	Full head alignment	Sitting	Stepping	Walking with assistance
Naïve analysis (Effective sample size: N=49)					
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 5 +	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Matching on sex, race and mutation (Effective sample size: N=1.16)					
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Year 2		[redacted]			[redacted]			[redacted]			[redacted]		
Year 3		[redacted]			[redacted]			[redacted]			[redacted]		
Year 4		[redacted]			[redacted]			[redacted]			[redacted]		
Year 5 +		[redacted]			[redacted]			[redacted]			[redacted]		
Matching on sex (Effective sample size: N=29.81)													
Baseline*		[redacted]			[redacted]			[redacted]			[redacted]		
Year 1		[redacted]			[redacted]			[redacted]			[redacted]		
Year 2		[redacted]			[redacted]			[redacted]			[redacted]		
Year 3		[redacted]			[redacted]			[redacted]			[redacted]		
Year 4		[redacted]			[redacted]			[redacted]			[redacted]		
Year 5 +		[redacted]			[redacted]			[redacted]			[redacted]		
Matching on sex and mutation (Effective sample size: N=17.20)													
Baseline*		[redacted]			[redacted]			[redacted]			[redacted]		
Year 1		[redacted]			[redacted]			[redacted]			[redacted]		
Year 2		[redacted]			[redacted]			[redacted]			[redacted]		
Year 3		[redacted]			[redacted]			[redacted]			[redacted]		
Year 4		[redacted]			[redacted]			[redacted]			[redacted]		
Year 5 +		[redacted]			[redacted]			[redacted]			[redacted]		
Matching on mutation (Effective sample size: N=23.73)													
Baseline*		[redacted]			[redacted]			[redacted]			[redacted]		
Year 1		[redacted]			[redacted]			[redacted]			[redacted]		
Year 2		[redacted]			[redacted]			[redacted]			[redacted]		
Year 3		[redacted]			[redacted]			[redacted]			[redacted]		
Year 4		[redacted]			[redacted]			[redacted]			[redacted]		
Year 5 +		[redacted]			[redacted]			[redacted]			[redacted]		

**Baseline is 24 months of age, in line with the age criteria used to define the N=49 NHDB population*
The highest motor milestone achieved at that timepoint is reported.

A30. Priority question: Please explain the rationales for selecting the three model specifications (company submission Section B.2.9.4.1). Could mutation status have been considered on its own or in combination with sex?

Company response:

Based on discussions at an advisory board with clinical experts in AADC deficiency[12] the Company decided not to use gene mutation alone as a factor for matching the populations. In addition, information on mutation was missing for 26.5% of patients in the NHDB. The missing patients are given a very small weight in the analysis, which is not reflective of the population.

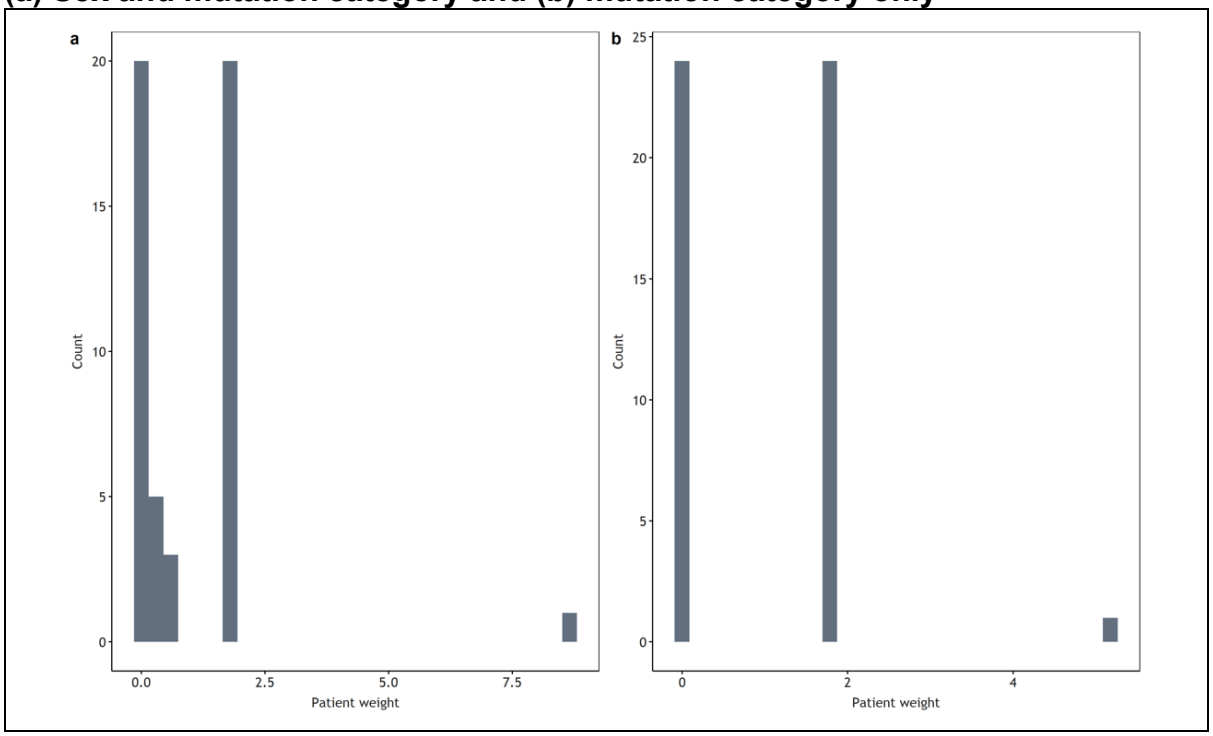
To address EAG question A30 and for completeness, Table 10 presents the effective sample sizes for all matching exercises, including when “sex and mutation category” and “mutation category alone” are used as covariates for matching. These analyses all yield small effective sample sizes. As presented in Figure 3, the resulting weights are dominated by one patient with a particularly large weight.

The distribution of patients across each motor milestone when matching by “sex and mutation category” and “mutation category alone” is presented in Table 9 in the response to question A29. In both specifications, motor milestone attainment estimates are lower than for the naïve analysis. For the purposes of the Company economic model, it therefore remains more conservative to use the naïve analysis than the matched analyses.

Table 10: Effective sample size results from the matching exercise

Matching variables	Effective sample size of NHDB
None	49
(a) Sex, race, mutation category	1.16
(b) Sex and race	8.08
(c) Sex	29.81
(d) Sex and mutation category	17.20
(e) Mutation category	23.73

Figure 3: Distribution of patient weights after the matching analysis for models (a) Sex and mutation category and (b) mutation category only



A31. Please clarify if the updated systematic review (company submission Section B.2.9.2) followed the same methodology as the Bergkvist 2021 poster.

Company response:

The SLR mentioned in Section B.2.9.2 of the Company submission followed a different methodology to the Bergkvist 2021[29] poster as the two SLRs were conducted for different purposes.

The SLR described in Bergkvist 2021 was conducted to identify all published cases of AADC deficiency. The data were used to develop a patient-level database for evaluating the natural history of AADC deficiency. The inclusion criteria for Bergkvist included case and case series reports, clinical studies of patients with diagnosed AADC deficiency, and literature reviews of publications and analyses of patients with AADC deficiency. The search criteria consisted of only AADC deficiency phrases.

The SLR mentioned in Section B.2.9.2 is described in Section B.2.1 and associated Appendices and was developed and conducted to meet NICE requirements[30] related to systematic searches for clinical efficacy and safety studies, cost-effectiveness studies, utilities, and cost and resource use outcomes. The SLR for the Company submission was therefore designed to capture a wider range of publication types and topics.

A32. Has the NHDB as presented in the Bergkvist 2021 poster been written up and submitted for publication? If so, please provide the paper.

Company response:

The Bergkvist 2021[29] poster is currently in the process of being drafted as a manuscript for publication. A draft is not yet available to share as it has not been submitted to any journals.

A33. Please provide the R code and individual participant data used for the population matching.

Company response:

The Company has provide the R code via email. The individual participant data for the analyses are not available to share.

A34. Please conduct a naïve indirect comparison of eladocagene exuparvovec versus best supportive care using the wider set of N=185 NHDB participants.

Company response:

The Company does not agree that it is appropriate to conduct a naïve indirect comparison using the N=185 population. The rationale for this is provided as follows:

- The N=185 population includes participants from the eladocagene exuparvovec trials (i.e. PTC participants). While it is appropriate to include these patients when describing the overall AADC deficiency population since they are described prior to being treated with eladocagene exuparvovec, there would be an overlap between the treatment groups when using the N=185 population as a comparator in a naïve analysis.

- Not all of the N=185 patients are appropriate for comparison with patients in the eladocagene exuparvovec studies. Of the N=185, only N=96 had sufficient information to determine disease severity. As a large proportion of the N=185 population do not have sufficient information to determine severity, and only N=49 were “non-PTC” patients (i.e. not in eladocagene exuparvovec studies) with a similar phenotype to patients in the eladocagene exuparvovec studies, the N=49 NHDB population is the only appropriate population to compare with the eladocagene exuparvovec population in a naïve analysis.

A35. Please clarify whether the studies included in the NHDB were quality assessed and with what quality assessment/critical appraisal tool. Please summarise the results of the quality assessment, if conducted.

Company response:

The Company did not conduct a formal quality assessment of the articles included in the NHDB, but the process used to identify unique subjects in the NHDB involved a review of the quality of information in each publication (as per Section 8 of the NHDB Data Management Plan).[31] In addition, a full quality check was performed of the NHDB (as per Section 6 of the NHDB Data Management Plan),[31] as well as an independent review of the information by the Quality Assurance department (as per Section 7 of the NHDB Data Management Plan).[31]

It should be noted that the publications contributing to the NHDB were not based on clinical studies, as no clinical studies had been performed in AADC deficiency prior to the eladocagene exuparvovec studies. All publications contributing to the NHDB are

case reports, case series, and review articles and the Company could not control how each publication collected and reported data or ensured data quality. All relevant information was extracted "as-is" from each publication.

A36. Priority question: Company submission, Section B.2.9.1.3, states "The NHDB initially identified 237 likely unique patients, of which 185 were unique patients with strong supporting data to be included in the final version of the NHDB. A total of 163 unique non-PTC subjects were identified." Please clarify what "strong supporting data" was needed for patients to be included in the NHDB. Please also clarify what "non-PTC subjects" means.

Company response:

To be identified as a unique patient, participants in the NHDB were required to have strong supporting data, meaning they could be:

- Identified directly and independently (i.e. uniquely identified subjects such as in Brun, 2010[32], or the subject had to be explicitly linked to subjects in other publications (e.g. a current publication link or reference to Brun, 2010[32])),
- Identified through deduction (i.e. the demographics and subject detail are available and match; the authors of institutions align; most demographics and subject detail attributes are available and match; or some demographics and subject detail attributes are available and match).

Based on the above, it was possible to identify patients in the NHDB who were involved in eladocagene exuparvovec studies (i.e. PTC subjects). "Non-PTC subjects" are those in the NHDB who were identified as not being patients participating in the eladocagene exuparvovec clinical trials (AADC-010, AADC-011, AADC-CU/1601).

A37. Please further clarify the reasons why the following studies listed in company submission, Section B2.9.2, Table 26, were excluded from the ITC feasibility analyses, as follows:

- **Pearson et al. (2020) and Saberian et al 2021 (company submission reference number 83) – reason: "Indirect information provided (clinician questionnaires), inferior to case reports utilised in NHDB". Please clarify if the clinician questionnaires included quantitative measures of motor**

function and why the questionnaires were considered to be inferior to case reports.

Company response:

Though the clinician questionnaire in Pearson *et al.* (2020)[20] includes quantitative measures of motor function, the online nature of the questionnaires, and the fact that they were combined with questionnaire answers from parents and caregiver, makes the measures of motor function less reliable than a case report.

The data from Saberian *et al.* (2021)[21] were reported in the form of a brief abstract, making it difficult to assess whether the questionnaire methodology and results obtained were robust. Therefore, it was conservatively excluded from the ITC feasibility analyses.

- **Saberian et al. (2021) (company submission reference number 81) and Williams et al. (2021) – reason: "Questionnaire data, inferior to case reports utilised in NHDB". Please clarify if the questionnaire data collected included quantitative measures of motor function and why questionnaire data were considered inferior to case reports.**

Company response:

The data from Saberian *et al.* (2021)[21] were reported in the form of a brief abstract, making it difficult to assess whether the questionnaire methodology and results obtained were robust. Therefore, it was conservatively excluded from the ITC feasibility analyses.

The data from Williams *et al.* (2021) were derived from a qualitative questionnaire and were therefore not deemed appropriate for use in the ITC feasibility analyses.

- **Wen et al. (2020) – reason: "Insufficient follow-up/long-term data for use in the NHDB". Please clarify if a measure of motor function was used in this study and at what timepoints follow-up/long-term data were collected.**

Company response:

Wen *et al.* (2020) was a genetic study in which there was only one mention of participants motor function, given at baseline. There was no follow-up or long-term data and therefore the data were not deemed appropriate for use in the analyses.

A38. Company submission, Section B.2.9.1.3, states that the motor milestones for each patient in the NHDB were "estimated through an assessment of the evidence reported in each publication related to quantitative motor function (using tools such as PDMS-2 and AIMS) and qualitative descriptions of individual patient development by the authors". It appears from Bergkvist et al. (2021) (company submission reference 8) that this process was carried out by two clinicians and was used to determine participants' disease phenotype. We have the following question about this: Was this estimate used to determine if participants had a similar phenotype to the trial population (AADC deficiency with no or poor head control at 24 months) and thus determined whether or not individual participants were included in the NHDB final sample of 49 people?

Company response:

Yes, this estimate was used to determine phenotype and to ensure that patients in the final sample of N=49 patients had a similar phenotype to the eladocagene exuparvovec trial population. The adjudication of severity was performed by two clinicians on a "per statement" basis, meaning that each individual statement regarding motor milestone was adjudicated individually and independently from other statements. The identification of the patients' individual phenotypes was also determined independently from other information (e.g., publication, author, disease progression), making the process impartial from individual interpretation.

The N=49 population constitutes patients in the NHDB who had a phenotype similar to patients in the eladocagene exuparvovec clinical trials (AADC deficiency with no or poor head control at 24 months) but who were "non-PTC" patients (i.e., patients not participating in clinical trials for eladocagene exuparvovec).

A39. Please summarise what measures of motor function were used from each study included in the NHDB to arrive at the motor milestone health state results presented in company submission, Section B.2.9.6, Table 29. Please

elaborate whether achievement of the milestones was directly extracted from the studies' data or whether achievement of the milestones was arrived at by an assessment of the data in each study by personnel involved in preparing the NHDB.

Company response:

Data related to motor function were extracted from each publication and inserted into the NHDB "as-is". Not all patients had explicit data related to achievement of motor milestones but had a description of their motor function.

For all patients in the NHDB, two independent clinical experts determined motor milestone achievement by reviewing the motor function descriptions extracted into the NHDB. To make the process impartial, the clinical experts were not members of the data entry team and they reviewed severity descriptions on a "per statement" basis independently of all other information related to the severity description (e.g. author, publication, other information related to the patient).

A40. Company submission, Section B.2.9.4, states that "For each patient in the NHDB, the motor development or milestone displayed at either the current visit or since the last visit was extracted from relevant publications where possible". Please clarify what "current visit or since the last visit" mean. Do these mean at the longest point of follow-up available in each study for each participant?

Company response:

Yes, this means the longest (or most recent) point of follow-up or observation for each participant. Generally, when referencing the NHDB, the term 'observation' or 'visit' was used instead of 'follow-up', as not all publications referred to an explicit period of follow-up.

A41. Please summarise the length of time participants in the NHDB had been receiving best supportive care up to the point where measures of their motor function were extracted for use in the NHDB.

Company response:

Data on the length of time participants in the NHDB had been receiving BSC up to the point where measures of their motor function were extracted for use in the NHDB were not consistently available across the publications in the NHDB and were therefore not extracted.

To respond to A41, the Company retrospectively reviewed the publications for the N=49 population. The length of time patients in the NHDB had been on BSC at the time of their motor function extraction ranged from 1–6 years for patients with available data. It should be noted that data were not reported or explicitly reported in all of the publications (e.g., there was mention of a follow-up period, but no mention of how long patients had received BSC treatment up to the point of measures of motor function).

A42. Priority question: Please summarise what best supportive care consisted in each of the studies from which data were included (for example, treatments, specialists and medical and technical procedures) in the Natural History Database. Please comment on the extent to which the care the participants received reflects that received by people with AADC deficiency in England.

Company response:

Best supportive care data were not collected routinely per publication within the NHDB, and the amount of information for each publication/patient varies. The available data per participant for the N=49 population are given in Table 11.

As mentioned in the Company submission, there are no UK-specific guidelines on the treatment of AADC deficiency, including from the National Institute for Health and Care excellence (NICE), NHS England, or other sources. In addition, the very low number of patients with AADC deficiency in the UK and the heterogeneous disease presentations means it is challenging to identify “typical” management of patients with AADC deficiency in the UK.

BSC is highly individualised and includes symptomatic treatments and support from a multidisciplinary team of specialists to address the profound symptoms, issues, comorbidities, and complications associated with the AADC deficiency.[6] Patients are managed with a varying and wide-ranging number of drugs and by a variety of specialists. The most commonly used treatments are those that target the dopamine pathway, including dopamine receptor agonists and monoamine oxidase (MAO)

inhibitors.[6] Patients also see a wide range of specialists as part of BSC, including paediatric neurologists, gastrointestinal specialists, endocrinologists, orthopaedic surgeons, speech therapists, pulmonologists, and physical and occupational therapists.[6] Outcomes for patients treated with BSC are reported in the consensus guideline by Wassenberg *et al.*[6] and Brun *et al.*[32] From the available data, disease progression is not attenuated in patients with AADC deficiency with arrested motor development.[3]

Clinical experts responsible for managing patients with AADC deficiency in the UK confirmed that the following therapies may be used: dopamine agonists (100% of patients), MAO inhibitors (100%), vitamin B6 (100%), anticholinergic agents (20-30%), benzodiazepines (40%), L-Dopa (10-20%), folic acid (80%), vitamin D (20%). This highlights the broad range of potential symptomatic treatments.

As mentioned in Table 11, in the NHDB, most patients received Vitamin B6 (pyridoxine), monoamine oxidase inhibitors, and dopamine agonists, and there was heterogeneity in the treatments prescribed across the patients with sufficient data. Compared with UK practice as outlined by the UK clinical expert above, BSC use in the NHDB broadly aligns with UK clinical practice as most patients in the NHDB used Vitamin B6 (pyridoxine), dopamine receptor agonists, and MAO inhibitors.

Table 11: Best supportive care among patients with severe phenotype as defined in the NHDB (N=49 population)*

	Best supportive care received prior to eladocagene exuparvovec treatment
1	Vitamin B6 (pyridoxine), selegiline, bromocriptine, L-Dopa, 5-hydroxytryptophan, trihexyphenidyl
2	NR
3	Laxatives, diazepam, Vitamin B6 (pyridoxine), selegiline, perfolide, L-Dopa, tranylcypromine, bromocriptine. Under the clinical suspicion of an extrapyramidal movement disorder a therapeutical trial of L-dopa (up to 15 mg per kg body weight) was used for 1 year without a clear clinical benefit.
4	Pyridoxine, tranylcypromine, bromocriptine, Vitamin B6, pyridoxal phosphate
5	Vitamin B6 (pyridoxine), pergolide, phenelzine and trihexyphenidyl but without clinical improvement, antiepileptics, pergolide, phenelzine, trihexyphenidyl
6	Vitamin B6 (pyridoxine), anticholinergics (akineton)
7	Dopamine agonist after diagnosis
8	Vitamin B6 (pyridoxine), dopamine agonist, anticholinergics
9	Vitamin B6 (pyridoxine), MAO inhibitor, dopamine agonists
10	Vitamin B6 (pyridoxine), dopamine agonists, anticholinergics
11	Vitamin B6 (pyridoxine), MAO inhibitors, dopamine agonist, anticholinergics
12	Bromocriptine, selegiline, pyridoxal phosphate, pergolide, MAO inhibitor, dopamine agonist
13	Pergolide, selegiline, pyridoxal phosphate, MAO inhibitor, dopamine agonist
14	NR
15	NR
16	Vitamin B6 (pyridoxine), bromocriptine
17	Vitamin B6 (pyridoxine), pergolide, selegiline
18	NR
19	L-DOPA, 5-OH-Trp, bromocriptine, selegiline, Vitamin B6 (pyridoxine), valproate, lamotrigine
20	Bromocriptine, Vitamin B6 (pyridoxine) in combination with valproic acid and clobazam for epileptic attacks

	Best supportive care received prior to eladocagene exuparvovec treatment
21	Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
22	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
23	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
24	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
25	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
26	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
27	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
28	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
29	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
30	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
31	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
32	Combination of Vitamin B6 (pyridoxine), dopamine agonists, and MAO inhibitors
33	Physical and occupational therapies
34	NR
35	NR
36	NR
37	NR
38	NR
39	NR
40	NR
41	Ropinirole, leucovorin, and pyridoxal-5'-phosphateoral hyoscyamine and scopolamine patches
42	NR
43	Pyridoxine, folinic acid, ropinirole, L-carnitine, clobazam
44	NR
45	NR
46	L-DOPA; MAO inhibitor
47	Vitamin B6 (pyridoxine), selective serotonin reuptake inhibitor
48	Vitamin B6 (pyridoxine), dopamine agonist, selective serotonin reuptake inhibitor
49	NR

Abbreviations: 5-OH-Trp – 5-hydroxy-L-tryptophan; MAO – monoamine oxidase; NR – Not reported
**Patients with no or poor head control at age 24 months (similar to the eladocagene exuparvovec study populations)*

A43. Please confirm all the study eligibility criteria (inclusion and exclusion criteria) that studies needed to meet to be included in the NHDB. Were any criteria used other studies needing to be case and case series reports and clinical studies of people diagnosed with AADC deficiency?

Company response:

The Company would like to clarify that the NHDB systematic searches were designed to identify publications that describe cases of AADC deficiency, rather than “clinical studies” of people diagnosed with AADC deficiency. The inclusion criteria for the NHDB were as follows:

- Case and case series reports of patients with diagnosed AADC deficiency.
- Clinical studies of patients with diagnosed AADC deficiency.
- Conference abstracts of patients diagnosed with AADC deficiency, if the data were not presented in a subsequent publication.

- Literature reviews of publications and analysis of subjects included with AADC deficiency.

Publications were excluded if they did not describe patient-specific clinical characteristics.

A few publications did not identify nor include individual subjects diagnosed with AADC deficiency, including detailed information such as:

- Describing potential treatments.
- Motor development or milestones.
- Symptomology.

In these cases, no subjects were included in the NHDB.

A44. Company submission, Section 1.3.2, states that "Diagnosis is usually achieved following confirmation from two of three tests: (1) analysing the pattern of cerebrospinal fluid (CSF), (2) monitoring AADC enzyme activity in plasma, and (3) genetic testing of the DDC gene. In the UK, 2 out of the 3 tests are required for a confirmed diagnosis, with genetic testing usually performed." For the NHDB, Bergkvist et al., states "Eligibility for inclusion of publications in the systematic review included case and case series reports and clinical studies of patients with diagnosed AADC deficiency". Did the eligibility criteria specify any particular method(s) of diagnosis? In particular, what method(s) of diagnosis was used for the 49 patients with severe AADC?

Company response:

The eligibility criteria for the NHDB did not require patients to have their AADC deficiency diagnosed via any specific methods of diagnosis and data were not explicitly extracted in the NHDB. If a publication explicitly stated that a patient was diagnosed with AADC deficiency then the patient was recorded in the NHDB. Depending on the data quality, information included, adjudication and deductions, the patient may be included in the final 237 unique subjects with diagnosed AADC deficiency in the NHDB.

To respond to question A44, the Company has retrospectively reviewed the 22 papers that comprised the evidence base for the 49 patients. Information on patient diagnosis

is given in Table 12. The methods of diagnosis for the 49 patients classified in the NHDB as having severe AADC deficiency (i.e. no or poor head control at 24 months, in line with the eladocagene exuparvovec study populations) were CSF, plasma analysis of AADC activity, urine analysis, blood spot screening, and genetic analysis. In most studies, a combination of methods was used, in line with UK practice. It should be noted that the NHDB includes patients diagnosed from 1990, and methods of diagnosis have evolved since then.

Table 12: Methods of diagnosis in publications in the NHDB (N=49;* 22 papers)

Publication	Method of diagnosis
Atwal et al., 2015[33]	A combination of CSF analysis and genetic analysis
Bankiewicz et al., 2019[17]	NR
Brun et al., 2010[32]	A combination of CSF, plasma analysis of AADC activity, and urine analysis
Dai et al., 2019[34]	Genetic analysis
Fiumara et al., 2002[35]	CSF analysis, plasma analysis of AADC activity
Helman et al., 2014[36]	CSF analysis, plasma analysis of AADC activity, genetic analysis/exome sequencing
Hwu et al., 2018[37]	A combination of CSF analysis and genetic/exome sequencing
Ide et al., 2010[38]	A combination of plasma analysis of AADC activity and genetic analysis/exome sequencing
Kojima et al., 2016[39]	NR
Kojima et al., 2019[40]	Plasma analysis of AADC activity, CSF analysis or exome sequencing
Kojima et al., 2017[41]	NR
Kojima et al., 2018[42]	NR
Korenke et al., 1997[43]	A combination of CSF analysis and plasma analysis of AADC activity
Lee et al., 2009[44]	Plasma analysis of AADC activity
Maller et al., 1997[45]	A combination of CSF, plasma analysis of AADC activity, and urine analysis
Manegold et al., 2009[46]	Plasma analysis of AADC activity
Osaka et al., 2019[47]	NR
Pons et al., 2004[48]	A combination of CSF analysis and plasma analysis of AADC activity
Spitz et al., 2017[49]	CSF analysis
Wang et al., 2019[50]	A combination of blood spot analysis and genetic analysis
Wassenberg et al., 2010[51]	A combination of CSF analysis, plasma analysis of AADC activity, and genetic analysis
Yamagata et al., 2016[52]	NR

Abbreviations: AADC – aromatic L-amino acid decarboxylase; CSF – cerebrospinal fluid; NHDB – natural history database; NR – not reported
Patients with no or poor head control by age 24 months (similar to eladocagene exuparvovec study participants)

A45. Please clarify if the motor milestone results in company submission, section B.2.9.6, Tables 29 and 30, only show the proportions of participants

who were classed as a) showing 'mastery' of the motor function or b) either showing 'newly emerging' abilities or 'mastery'.

Company response:
The motor milestone results in Tables 29 and 30 show the proportion of patients who were classed as (b) either showing 'newly emerging' abilities or 'mastery'.

A46. Please provide the participant numbers results for company submission, Section B.2.9.6, Table 29, in addition to the proportions already included in the table.

Company response:
The NHDB is based on a systematic literature review of published cases of AADC deficiency as of December 2019. As such, it relies on the data available for each patient in the publications.

Due to the nature of how the NHDB was collected, and that it was reliant on publications being presented on these patients at multiple timepoints, there is limited longitudinal data. For those where there is some longitudinal data, there are limited data points (e.g. a patient may have 4 years of follow-up data but that does not mean that there are relevant data at each year within the 4-year follow-up period). Therefore, to estimate motor milestone achievement for the BSC arm, the Company assumed that patient motor milestones progress linearly between time points up to the last follow-up point. The Company also assumes the last observation is carried forward for patients in the NHDB.

It should be noted that in the NHDB, only 2 of 49 patients were recorded as experiencing any motor milestone attainment over their follow-up period. One patient achieved walking with assistance at Year 2 (their last recorded follow-up) and one achieved sitting at Year 3. This lack of motor milestone attainment following BSC in the vast majority of patients with severe AADC deficiency is in line with the published literature (e.g. Wassenberg *et al.*[6] and Brun *et al.*[32]).

The participant numbers for the motor milestone health states in the BSC arm of the Company submission are presented in Table 13.

Table 13: Distribution of patients across motor milestone health states in the BSC arm (derived from the NHDB)

	No motor milestone N (%)	Full head alignment N (%)	Sitting N (%)	Stepping N (%)	Walking with assistance N (%)
Baseline	49 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Year 1	48 (98%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Year 2	47 (96%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Year 3	47 (96%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Year 4	47 (96%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Year 5 +	47 (96%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)

Abbreviations: BSC – best supportive care; NHDB – natural history database
**Baseline is 24 months of age, in line with the age criteria used to define the N=49 NHDB population*

Section B: Clarification on cost-effectiveness data

Clinical parameters

B1. Priority question: Regarding the company's approaches for predicting motor milestones for their cost effectiveness analysis (as detailed in company submission, Section B.3.3.1.1.1), we have the following requests and questions:

(a) Please clarify the rationale for using:

(i) Bayesian growth curve modelling of the observed trial data to predict PDMS-2 score over time; please explain why this method was preferred over the other longitudinal modelling techniques such as multilevel modelling.

Company response

The Bayesian growth models were chosen over other longitudinal modelling techniques for several reasons.

A Bayesian approach has been taken as it has the advantage of being able to easily present inferences which fully consider uncertainty about all unknown quantities, including the extent of between-patient heterogeneity. Further, a Bayesian approach allows for the full maximisation of the available data. This is particularly important due to the small sample size (N=28), where different model specifications can place large

burdens on the available data and lead to the overfitting and/or non-convergence of models.

Expert clinical opinion suggested that the shape of the Bayesian curves was likely to plateau over time, and so that fed into the initial specification through the choice of model forms. By making the decision based on model form, it meant that there was a focus on models that met that specific form. This allowed for full use of the data on the parameters that reflected the shape of that model form, as opposed to also relying on the data to estimate the form of the model.

This Bayesian growth modelling approach also facilitated in capturing the underlying information on a patients' PDMS-2 score in their subsequent likelihood of meeting a motor milestone. Some patients were still increasing in PDMS-2 scores at the time of their last follow-up but had not yet achieved the next key motor milestone. A Bayesian approach enables the model to capture the fact that these patients are more likely to reach their next motor milestone in the future, as suggested by their increasing PDMS-2 score, and carry this clinical efficacy through the developmental phase of the CEA.

Bayesian growth curve modelling of the observed trial data is, in essence, a form of multilevel modelling. In multilevel modelling an overall change function (dependent on time) is fitted to the whole population but random effects on the slope and intercept are allowed to differentiate between different patients. This is what the Bayesian growth models are doing – we assume that all patients have a trajectory that follows the general growth trajectory of the model form (i.e. Gompertz, asymptotic, logistic). Due to our assumptions and understanding of how patients' trajectories vary, the intercept (the baseline PDMS-2 value), the slope, and the final value (the model asymptote) are allowed to vary between patients. The Company believes that having the flexibility to allow these values to vary in the model is important to reflect the true pathway of the patient PDMS-2 scores.

The Company did consider a longitudinal modelling approach, where motor milestone state membership was modelled directly (i.e. through a cohort state transition model), but it was considered inappropriate for several reasons. Longitudinal modelling does not use all available data, which is particularly important in this case due to the limited patient numbers. Through fitting the PDMS-2 scores with the Bayesian model, we

capture “within motor milestone state” movements meaning that we can be more sensitive to the treatment effect and predicting motor milestone improvements that have not yet been observed. This is of interest as there are cases where patients have a large increase in PDMS-2 score but do not meet the next motor milestone state. Additionally, it is clear from the data that patient’s progression across motor milestone states over time is not constant, and so time-dependent transition probability matrices would be needed, which would make the longitudinal modelling approach complex. This is a further limitation of longitudinal modelling compared to Bayesian growth modelling.

Therefore, a Bayesian growth approach was the preferred method over other longitudinal modelling techniques in predicting PDMS-2 scores over time. In an economic model validation held with HEOR experts on March 2021[53], all of the of the respondents (N=6) agreed that the Bayesian growth model approach was reasonable.

(ii) a cumulative ordered logit model to estimate motor milestones based on the predicted PDMS-2 scores.

Company response

The relationship between the PDMS-2 and the attainment of motor milestones is not a 1:1 relationship (see the response to B1(e) for further information). This means it is possible for patients with the same PDMS-2 scores to have achieved different motor milestones. Therefore, it is not possible to derive a patient’s motor milestone deterministically from their PDMS-2 score, so a predictive modelling approach is required to capture the uncertainty between the two measures through error terms.

The cumulative ordered logit model specification was chosen as it matches the dependent data structure that is in the data. Namely, that the meeting of motor milestones is a set of discrete ordered outcomes. In the fitting of these models, the observed data from the PDMS-2 at each timepoint were used to fit the cumulative ordered logit models. When incorporating the results of this two-step modelling approach into the economic model, the predicted PDMS-2 values from the growth equations were used to estimate the likelihood of each patient having reached each motor milestone.

(b) Was a sensitivity analysis conducted on the choice of vague priors in the Bayesian model?

Company response

A sensitivity analysis was not carried out on the choice of vague priors in the model. Due to the limited information in AADC deficiency and the small sample size in the trials (N=28) there is little information available on which to base the priors on and hence vague priors were used. The priors were chosen to not be overly restrictive but represent plausible options for the parameter values.

(c) Was age the only covariable included in the Bayesian model? If so, please justify.

Company response

The clinical data suggest that the age of patients at baseline may influence the rate of improvement of PDMS-2 scores following eladocagene exuparvovec treatment. As demonstrated in Company submission Section J.1.1 Figure 58, age at baseline is heterogeneous in the eladocagene exuparvovec trial populations. Clinical experts agreed that age at baseline would be an important predictor of motor milestone achievement at an Advisory board (February 2020).[54] Furthermore, due to the small sample size of the trial population, the addition of too many variables to the model specifications risked the models over fitting or not converging at all. Therefore, the Company considered it appropriate to include age as the only covariable in the Bayesian growth model specifications.

Within the model specifications for the Gompertz, asymptotic and logistic models, the parameters in each model were assumed to take a linear form, where each parameter had an age independent component and age dependent component. Details of the exact model specifications can be found in the Company submission Section J.1.3.3.

(d) Please clarify if these approaches have been used in previous NICE appraisals.

Company response

NICE has not previously undertaken any appraisals in the ultra-rare condition of AADC deficiency. As such, the Company is not aware of any previous NICE appraisals that

used a similar approach. In an Economic advisory board (March 2021[53]), consisting of eight HEOR experts (two from the UK), all participants agreed that the approach used by the Company was appropriate for modelling AADC deficiency.

(e) Please clarify how the PDMS-2 scores were grouped to match the motor milestone categories.

Company response

Motor milestones were defined through the responses in PDMS-2 questions across the three eladocagene exuparvovec trials as follows:

Full-head control

The patient achieves a score of at least 1 on item #10 of the stationary (gross motor) subscale, i.e., the patient can sit supported at their hips and holding their head aligned while rotating their head to follow a toy for at least 4 seconds.

Sitting unassisted

The patient achieves a score of at least 1 on Item #14 of the stationary (gross motor) subscale, i.e., the patient is required to sit without support for at least 30 seconds.

Stepping/standing with support

The patient achieves a score of at least 1 on Item #28 of the locomotion (gross motor)' subscale, i.e., the patient is able to take at least 2 alternating steps with support around the trunk.

Walking with assistance

The patient achieves a score of at least 1 on Item #34 of the locomotion (gross motor) subscale, i.e., the patient can walk at least 4 feet with alternating steps with minimal support.

No motor function

A patient was considered as having achieved no motor milestones (i.e., no motor function) if they had a score of 0 on all of the items described above for the other motor milestone categories.

Patients score a “1” when they have partially mastered a skill but have yet to meet the strict criteria for a score of 2 (mastery). For example, to have partially mastered “walking with assistance”, the patient can walk at least 4 feet but less than the 8 feet stipulated in the PDMS-2 scoring system.

Due to the nature of the PDMS-2 scoring (please refer to question A8 for more detail) it is possible for patients with the same PDMS-2 total score to have differing levels of motor milestone attainment. It is this heterogeneity between motor milestone attainment and PDMS-2 total scores that the cumulative ordered logit model is capturing through the different probabilities of being in each motor milestone state.

(f) Please could you provide patient level data collected in the clinical trials for- PDMS-2 scores, motor milestone outcomes and Bayley III scores.

Company response

Unfortunately, the individual participant data collected in the clinical trials for PDMS-2 scores, motor milestone outcomes, and Bayley III scores are not available to share.

(g) Please provide the R code used for the Bayesian growth curve and logistic modelling.

Company response

The Company has provided the R code via email.

B2. Please provide a scenario analysis considering the moderate and severe treatment emergent adverse events (TEAEs) occurring in >5% of patients up to Month 12.

Company response:

A scenario analysis was run to include all moderate-to-severe TEAEs occurring in >5% of patients receiving eladocagene exuparvovec up to Month 12 of follow-up. The annual rate of TEAEs in the CEA occurring in >5% of patients receiving eladocagene exuparvovec are presented in Table 14.

As stated in the original company submission, moderate-to-severe TEAEs in the CEA are applied to the eladocagene exuparvovec arm only as similar information is not available for patients in the BSC arm. The CEA therefore conservatively assumes that TEAEs with BSC are set to 0% for each event and instead are captured in the disease management costs.

Table 14: Moderate-to-severe TEAEs occurring in >5% patients at 12 months post-eladocagene exuparvovec across the three pivotal trials (N=28)

Adverse event	Eladocagene exuparvovec	
	Moderate	Severe
Dyskinesia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Hypovolaemic shock	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Cyanosis	[redacted]	[redacted]
Pneumonia influenzal	[redacted]	[redacted]
Post procedural pneumonia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Initial insomnia	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]

TEAEs occurring in the trials were coded per the MedDRA coding dictionary version 23; Severity of adverse events was determined by the investigator. TEAE rates taken from May 2020 Integrated Summary of Safety files.
TEAE – treatment emergent adverse event
Source: Integrated summary of safety data tables (Table 2.12), May 2020[55]

A disutility value is applied to each of the moderate-to-severe TEAEs occurring in >5% of patients receiving eladocagene exuparvovec apart from dehydration and initial insomnia. These TEAEs do not have a disutility value as they are captured within the five health state vignettes used to derive the health state utility values in the time trade-off (TTO) method used in the base-case CEA. Initial insomnia is assumed to already be captured within the symptoms associated with sleep, and dehydration is assumed to already be captured within the symptoms associated with feeding and swallowing problems within the five health state vignettes.

Disutility values for the TEAEs were identified through a targeted literature review and are presented, along with the associated sources, in Table 15. In the targeted literature review to identify disutility values for the TEAEs, a more appropriate disutility value for pneumonia was identified from NICE guidelines and instead has been used to replace the original disutility value for pneumonia (which was assumed to be equal to asthma).

In the absence of evidence on duration of TEAEs, it was conservatively assumed that symptoms of TEAEs lasted for up to 60 days.

Table 15: TEAE disutility values used in the scenario for moderate-to-severe TEAEs occurring in >5% of patients receiving eladocagene exuparvovec

Adverse event	Disutility	Source	Duration (days)
Dyskinesia	0.0669	Sullivan et al. (2011)[56], assumed equal to epilepsy, convulsions	60
Pneumonia	0.13	NICE guideline NG115[57]	60
Gastrointestinal disorders	0.0512	Sullivan et al. (2011) [56], assumed equal to "other gastrointestinal disorders"	60
Gastroenteritis	0.0725	Sullivan et al. (2011)[56], assumed equal to non-infectious gastroenteritis	60
Hypotension	0.070	NICE TA783[58]	60
Hypovolaemic shock	0.063	Sullivan et al. (2011)[56], assumed equal to circulatory disease	60
Pyrexia	0.110	Beausterien *et al.* (2010)[59]	60
Cyanosis	0.13	NICE guideline NG115[57], assumed equal to pneumonia	60
Pneumonia influenzal	0.13	NICE guideline NG115[57], assumed equal to pneumonia	60
Post procedural pneumonia	0.13	NICE guideline NG115[57], assumed equal to pneumonia	60
Upper respiratory tract infection	0.190	NICE TA783[58]	60
Dehydration	0.000	No disutility applied. Utilities captured in the vignettes.	60
Initial insomnia	0.000	No disutility applied. Utilities captured in the vignettes.	60
Respiratory failure	0.13	NICE guideline NG115[57], assumed equal to pneumonia	60

Abbreviations: TEAE – treatment-related adverse event

The costs associated with the TEAEs occurring in >5% of patients receiving eladocagene exuparvovec are presented in Table 16, with a different cost for moderate and severe events. The cost associated with the event of dehydration have been assumed to be £0. This is following the NICE guidelines (CG84)[60] that dehydration should be treated with oral rehydration salts for which the costs are negligible. The costs of TEAEs are sourced from the National Schedule of Reference Costs 2019/2020.[61]

Table 16: Moderate-to-severe TEAE costs occurring in >5% of patients receiving eladocagene exuparvovec

Adverse event	Moderate TEAE cost	Severe TEAE cost	Source

Dyskinesia	£3,492.73	£5,313.86	National Schedule of Reference Costs 2019/2020 cost for Paediatric Nervous System Disorders, weighted by day case / non-elective short stay by the proportion requiring hospitalisation for moderate and severe dyskinesia (PR01A:E) Moderate: 55% of cases require hospitalisation. Severe: 100% of cases require hospitalisation
Pneumonia	£1,414.61	£2,437.31	National Schedule of Reference Costs 2019/2020: cost for pneumonia (DZ11R and DZ11S for severe and DZ11T and DZ11U for moderate) Moderate: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-9 Severe: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10+
Gastrointestinal disorders	£597.67	£614.03	National Schedule of Reference Costs 2019/2020: day case cost for paediatric gastrointestinal (GI) disorders (PF26A and PF26B for severe and PF26C and PF26D for moderate) Moderate: Paediatric Major Gastrointestinal Disorders with CC Score 1-4 Severe: Paediatric Major Gastrointestinal Disorders with CC Score 5+
Gastroenteritis	£489.90	£565.79	National Schedule of Reference Costs 2019/2020: day case cost for paediatric gastroenteritis (PF21A,PF21B) Moderate: Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 0 Severe: Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 1+
Hypotension	£1,261.20	£1,556.71	National Schedule of Reference Costs 2019/2020: day case cost for Paediatric Cardiac Conditions (PE23A and PE23B for severe and PE23C and PE23D for moderate) Moderate: weighted costs of Paediatric Cardiac Conditions with CC score 3-5 and Paediatric Cardiac Conditions with CC score 6-9 Severe: weighted costs of Paediatric Cardiac Conditions with CC score 10-12 and Paediatric Cardiac Conditions with CC score 13+
Hypovolaemic shock	£1,261.20	£1,556.71	National Schedule of Reference Costs 2019/2020: day case cost for Paediatric Cardiac Conditions (PE23A and PE23B for severe and PE23C and PE23D for moderate) Moderate: weighted costs of Paediatric Cardiac Conditions with CC score 3-5 and Paediatric Cardiac Conditions with CC score 6-9 Severe: weighted costs of Paediatric Cardiac Conditions with CC score 10-12 and Paediatric Cardiac Conditions with CC score 13+
Pyrexia	£957.09	£1,602.77	National Schedule of Reference Costs 2019/2020: cost for Paediatric Fever of Unknown Origin (PW20A for severe and PW20B for moderate) Moderate: National Schedule of Reference Costs 2019/2020: cost for Paediatric Fever of Unknown Origin Severe: Paediatric Fever of Unknown Origin with CC score 3+ (PW20A)
Cyanosis	£1,261.20	£1,556.71	National Schedule of Reference Costs 2019/2020: day case cost for Paediatric Cardiac Conditions (PE23A and PE23B for severe and PE23C and PE23D for moderate) Moderate: weighted costs of Paediatric Cardiac Conditions with CC score 3-5 and Paediatric Cardiac Conditions with CC score 6-9

			Severe: weighted costs of Paediatric Cardiac Conditions with CC score 10-12 and Paediatric Cardiac Conditions with CC score 13+
Pneumonia influenzal	£1,414.61	£2,437.31	National Schedule of Reference Costs 2019/2020: cost for pneumonia (DZ11R and DZ11S for severe and DZ11T and DZ11U for moderate) Moderate: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-9 Severe: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10+
Post procedural pneumonia	£1,414.61	£2,437.31	National Schedule of Reference Costs 2019/2020: cost for pneumonia (DZ11R and DZ11S for severe and DZ11T and DZ11U for moderate) Moderate: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-9 Severe: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10+
Upper respiratory tract infection	£855.56	£1,930.00	National Schedule of Reference Costs 2019/2020: cost for paediatric Upper Respiratory Tract disorders (PD65A for severe and PD65C PD65B and PD65C for moderate) Moderate: Paediatric Upper Respiratory Tract Disorders with CC Score 1 and Paediatric Upper Respiratory Tract Disorders with CC Score 2-4 Severe: Paediatric Upper Respiratory Tract Disorders with CC Score 5+
Dehydration	£0.00	£0.00	Assumption. The costs for treatment with oral rehydration salts, as recommended in NICE guidelines (CG84)[60], are negligible.
Initial insomnia	£424.18	£795.54	National Schedule of Reference Costs 2019/2020: cost for Sleep Disorders, excluding Sleep Apnoea (AA43A for severe and AA43B for moderate) Moderate: Sleep Disorders, excluding Sleep Apnoea, with CC Score 0-1 Severe: Sleep Disorders, excluding Sleep Apnoea, with CC Score 2+
Respiratory failure	£1,449.83	£2,386.48	National Schedule of Reference Costs 2019/2020: cost for Respiratory Failure without Interventions (DZ27S for severe and DZ27T for moderate) Moderate: Respiratory Failure without Interventions, with CC Score 6-10 Severe: Respiratory Failure without Interventions, with CC Score 11+ re 6-10

Abbreviations: NHS – National Health Service; TEAE – treatment-emergent adverse events
Source: National Schedule of Reference Costs 2019/2020[61]

The results of the scenario analysis for including moderate-to-severe TEAEs occurring in >5% of patients receiving eladocagene exuparvovec are presented in Table 17 and Table 18 for the list price and PAS price, respectively. Note that the base-case results include the combined updates related to B12, B13, B14, B19, B20 and B21. The changes have a minimal impact on the original ICERs in the Company submission, which were £176,343 at list price and £[redacted] at PAS price.

Table 17: Scenario results of including moderate to severe TEAEs occurring in >5% of patients receiving eladocagene exuparvovec (list price)

Setting	TEAE threshold	Incremental costs	Incremental QALYs	ICER
Base case	20% of patients	[redacted]	[redacted]	£176,617
EAG question B2 scenario	>5% of patients	[redacted]	[redacted]	£177,054

ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life year TEAE – Treatment-emergent adverse event

Table 18: Scenario results of including moderate to severe TEAEs occurring in >5% of patients receiving eladocagene exuparvovec (PAS price)

Setting	TEAE threshold	Incremental costs	Incremental QALYs	ICER
Base case	20% of patients	[redacted]	[redacted]	[redacted]
EAG question B2 scenario	>5% of patients	[redacted]	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; PAS – Patient Access Scheme; QALY – Quality-adjusted life year; TEAE – Treatment-emergent adverse event

B3. Company submission, Section B.3.3.2.2, states that a pragmatic literature review was conducted to identify proxy diseases to estimate long-term survival for AADC deficiency. Please would you:

(a) provide the methods, search strategies and eligibility criteria used and the results from the review

Company response:

A pragmatic literature search was carried out to determine suitable proxy diseases with similar disease profiles to AADC deficiency.[62] The search criteria used for identifying the relevant proxy diseases based on relationship between motor milestone achievement and HRQoL can be seen below in Table 19.

Table 19: Search criteria for identifying relevant proxy diseases for AADC deficiency

Categories	Search terms
Population	• Paediatric patients or paediatric population • Newborns • Infants • Children • (Early) Childhood
Disease	• Neurological conditions • Neurological diseases or pathologies • Genetic disease • Inherited disease
Treatments	• Gene therapy • Stem cell treatment
Endpoints	• Motor development

Outcomes	• Motor milestones • Developmental milestones • Motor delay
Study design	• Observational studies • Single arm clinical trials • Randomised clinical trials • Systematic reviews • Case studies or case reports
Time span	• January 2015 – January 2020
Databases	• Clinicaltrials.gov • PubMed.gov

Based on the pragmatic literature search, type 1 spinal muscular atrophy (SMA) and cerebral palsy (CP) were identified as the best proxy diseases due to their similar disease profile to AADC deficiency and because they provide survival estimates by motor milestone health state.

In addition to the pragmatic literature search, clinical experts also identified the following potentially relevant neurotransmitter diseases as suitable proxies (Clinical Advisory Board 1, February 2020[54] and internal PTC clinical experts): anoxic encephalopathy, paraplegia, tyrosine hydroxylase (TH) deficiency, guanosine triphosphate cyclohydrolase (GTPCH) deficiency, sepiapterin reductase (SR) deficiency, and dopamine transporter (DAT) deficiency syndrome. The Company used the following criteria to assess whether any of these additional neurotransmitter-related diseases were suitable proxies for survival in AADC deficiency:

- Disease pathology occurring since early childhood,
- Non-degenerative nature of the disease,
- Presence of other symptoms, e.g., OGC, cognitive impairment.

An overview of the proxies considered and how they relate to the criteria listed above is presented in Table 20. Of the additional proxies explored (i.e other than CP and SMA), only anoxic encephalopathy and TH deficiency had potentially similar survival estimates to AADC deficiency (from the limited available data for both conditions). Unfortunately, both anoxic encephalopathy and TH deficiency lacked relevant published long-term mortality data (i.e. related to motor milestone health state), so scenario analyses were not carried out in the economic model for these proxies.

Based on the above, and after consultation with clinical experts at a Clinical Advisory Board 1 (February 2020[54]), within two online surveys with more than 20 international experts (Clinical survey, June 2020[63]), the closest proxy to AADC deficiency was "true" or "classical" CP. Thus, survival estimates from CP are used as a proxy to map onto the motor milestone states used in the model. CP was deemed by clinical experts, including those in the UK, to be a more suitable proxy for survival than SMA Type I. SMA Type I was considered to be less suitable as it is a very severe, progressive, degenerative disease and does not include dystonia and autonomic instability. SMA Type I was therefore used as a scenario analysis. These were the only proxies used for estimating long-term survival in the Company economic model.

Survival in the Company submission is modelled as a common clinical parameter and depends only on patient motor milestone state (i.e., not on treatment received). Thus, the differential effect of treatment on survival is driven by its impact on motor milestone attainment. This is similar to the approach accepted by NICE for Zolgensma in SMA Type 1 (HST15).[64]

Table 20: Summary of proxy diseases to estimate survival for AADC deficiency trial population

Proxy disease	Occurring in early childhood (≤12 months)	Degenerative pathology	Points of similarity with AADC deficiency trial population	Included in economic model?
Classical CP	Yes	No	Age at onset, developmental delay, motor impairment, dystonia, feeding issues, cognitive impairment, language impairmant	Base case
SMA Type I	Yes	Yes	Age at onset, motor impairment, hypotonia, feeding issues	Scenario
Anoxic encephalopathy	Hypoxic ischaemic encephalopathy	No	Neurologic abnormalities (motor and cognitive impairment including behavioural issues)	No
Paraplegia	Hereditary spastic paraplegia	Yes	Motor functioning issues	No
TH deficiency	TH-Deficient infantile parkinsonism with motor delay; TH-Deficient progressive infantile encephalopathy	No	Age at onset is within 12 months, motor developmental delay, OGC, autonomic dysfunction and feeding abnormalities	No
GTPCH deficiency	-	Yes	Dystonia	No

Proxy disease	Occurring in early childhood (≤12 months)	Degenerative pathology	Points of similarity with AADC deficiency trial population	Included in economic model?
SR deficiency	Yes	Yes	Age at onset is approximately 12 months	No
DAT deficiency	Infantile parkinsonism-dystonia	Yes	Age at onset is approximately 12 months; patients present with walking and feeding difficulties	No

Abbreviations: AADC – Aromatic L-amino acid decarboxylase; CP – cerebral palsy; DAT - dopamine transporter; GTPCH - guanosine triphosphate cyclohydrolase; OGC – Oculogyric crises; SMA – spinal muscular atrophy; SR – Sepiapterin reductase; TH – Tyrosine hydroxylase

(b) clarify if the study by Brooks et al. 2014 was identified as part of the above pragmatic literature review to inform AADC deficiency survival.

Company response:

The Brooks *et al.* (2014)[65] paper was not identified as part of the pragmatic literature review described above as the pragmatic literature review was for publications from January 2015 to January 2020.

The Brooks *et al.* (2014)[65] paper was identified following discussions with clinical experts highlighted that classical CP was the most appropriate proxy disease for survival in the economic model. Once classical CP had been identified, a targeted literature review was undertaken to identify appropriate studies to populate the model. It was through this targeted review that the Brooks *et al.* (2014)[65] paper was identified. The Brooks study was selected because of its large sample size and its use to model mortality in a cost-effectiveness model for a 2018 NICE guideline on the management of abnormal muscle tone (dystonia). The NICE guideline authors concluded that Brooks et al. (2014)[65] provided “up-to-date” survival estimates and that the Californian population was generalisable to England and Wales, highlighting the robustness of the data."

B4. Priority question: Regarding the justification for using the Gompertz model to predict PDMS-2 scores in the Bayesian growth model detailed in company submission, Section B.3.3.1.1.3, for completeness and clarity, please also provide the fit of logistic models to predict PDMS-2 scores in the Bayesian growth model, like company submission Figure 64. Please also conduct a

scenario analysis using logistic models in the Bayesian growth model and explore its impact on the overall cost-effectiveness results.

Company response:

The logistic model was not included in the final model and initial submission as it was found that it did not converge and fit the data as well as the other two models included (Gompertz [base-case] and asymptotic [scenario analysis]). The fit of the logistic model (Figure 4) compared with the Gompertz model shows that the logistic model has a very poor fit to the data. In some cases, the logistic model was unable to fit properly formed logistical growth curves (as can be seen from the sharp inflection points and high initial values). This is particularly evident in the case where there is a small amount of follow-up data for the patients.

For these reasons, this model specification was not considered appropriate for inclusion in the economic model and a scenario analysis has not been carried out using the logistic model in the Bayesian growth model.

Figure 4: Results of fitting the logistic and Gompertz model to the PDMS-2 scores (N=28 population treated with eladocagene exuparvovec)

**black line represents observed data*

B5. Priority question: Company submission, Section B.3.3.2.3, states "Survival data were therefore extrapolated using parametric curves fitted to each motor milestone state. The Gompertz, Weibull, log normal, log logistic, gamma, and exponential models were fitted to survival data for each motor milestone health state, based on information in NICE DSU 14." However, no further information (diagram or statistical values) is provided. Please provide the AIC and BIC values for all the fitted parametric curves. Please also present all the fitted survival curves (and not the only ones deemed as best fits) diagrammatically for different motor milestone health states.

Company response:

The AIC and BIC values for all parametric curves fitted to each motor milestone health state using data from the Brooks *et al.* (2014)[65] study for patients with cerebral palsy (CP) are presented in Table 21. The term "Not defined" in the coefficients column relates to parametric curves that did not converge for the corresponding motor milestones. In these cases, the AIC and BIC values are not presented.

Table 21: Coefficients and goodness of fit statistics for the survival analysis using data from Brooks *et al.* (2014)[65]

Motor milestone health state		Coefficients	AIC	BIC
No motor function				
Exponential	Rate	0.0483 (0.036, 0.061)	-12.22	-12.32
Weibull	Scale Shape	17.736 (17.275, 22.196) 1.477 (1.001, 1.952)	-17.98	-18.14
Gompertz	Rate Shape	0.031 (0.010, 0.053) 0.041 (-0.015, 0.097)	-14.11	-14.27
Log Normal	Logmean Sdlog	2.689 (2.615, 2.762) 0.775 (0.642, 0.908)	-27.14	-27.30
Log logistic	Shape Scale	2.136 (1.697, 2.575) 14.732 (13.48, 15.98)	-25.05	-25.22
Gamma	Shape Rate	1.9846 0.1092	-25.06	-25.22
Full-head control				
Exponential	Rate	0.022 (0.017, 0.027)	-17.40	-17.51
Weibull	Scale Shape	34.467 (31.707, 37.226) 1.625 (1.360, 1.890)	-32.69	-32.85
Gompertz	Rate Shape	Not defined Not defined	NA	NA
Log Normal	Logmean Sdlog	Not defined Not defined	NA	NA
Log logistic	Shape Scale	1.981 (1.736, 2.227) 27.556 (26.269, 28.843)	-36.72	-36.88
Gamma	Shape Rate	Not defined Not defined	NA	NA
Sitting unassisted				
Exponential	Rate	0.014(0.011, 0.018)	-18.69	-18.79
Weibull	Scale Shape	41.378 (38.203, 44.553) 1.876 (1.624, 2.128)	-39.10	-39.26
Gompertz	Rate Shape	Not defined Not defined	NA	NA
Log Normal	Logmean Sdlog	Not defined Not defined	NA	NA
Log logistic	Shape Scale	2.147 (1.788, 2.506) 35.133 (32.421, 37.845)	-36.16	-36.32
Gamma	Shape Rate	Not defined Not defined	NA	NA
Standing with support				
Exponential	Rate	0.004 (0.003, 0.005)	-34.98	-35.09
Weibull	Scale Shape	86.173 (77.181, 96.165) 1.792 (1.641, 1.944)	-61.04	-61.20

Gompertz	Rate Shape	Not defined Not defined	NA	NA
Log Normal	Logmean Sdlog	Not defined Not defined	NA	NA
Log logistic	Shape Scale	1.870 (1.718, 2.022) 79.310 (71.804, 86.816)	-61.56	-61.72
Gamma	Shape Rate	Not defined Not defined	NA	NA
Walking with assistance				
Exponential	Rate	0.002 (0.001, 0.003)	-34.73	-34.83
Weibull	Scale Shape	62.999 (56.162, 69.837) 3.305 (2.869, 3.741)	-63.18	-63.34
Gompertz	Rate Shape	0.342 (Not defined) -12.370 (Not defined)	-24.73	-24.90
Log Normal	Logmean Sdlog	Not defined Not defined	NA	NA
Log logistic	Shape Scale	3.384 (2.913, 3.853) 61.152 (54.394, 67.911)	-62.47	-62.63
Gamma	Rate	Not defined Not defined	NA	NA

Parametric survival curves are presented diagrammatically in Figure 5. Survival in the Company economic model was adjusted for background mortality based on England and Wales general population mortality from the Office for National Statistics. Each survival curve that converged was fitted to each motor milestone health state.

In terms of goodness of fit statistics only, the log normal model fits the data best for no-motor function; the log logistic model for full-head control; Weibull for sitting unassisted; log logistic for standing with support and Weibull for walking with assistance. However, as stated in the Company submission, based on the crossing of curves for different motor milestone health states, selecting survival curves based only on individual AIC and BIC values for each motor milestone health state was not plausible or optimal for this CEA. Therefore, the curves were assessed for statistical fit, visual fit and clinical plausibility. While the log logistic curve had the best overall statistical fit across all milestones (with AIC and BIC values of -221.96 and -222.77, respectively), it resulted in crossing of curves for the “walking with assistance” and “standing with support” curves. The exponential curve was therefore selected for the “walking with assistance” health state as part of the base-case as it was the next-best-fitting curve that did not cross with the other motor milestone health state curves. The log-logistic curve was selected for the four remaining health states.

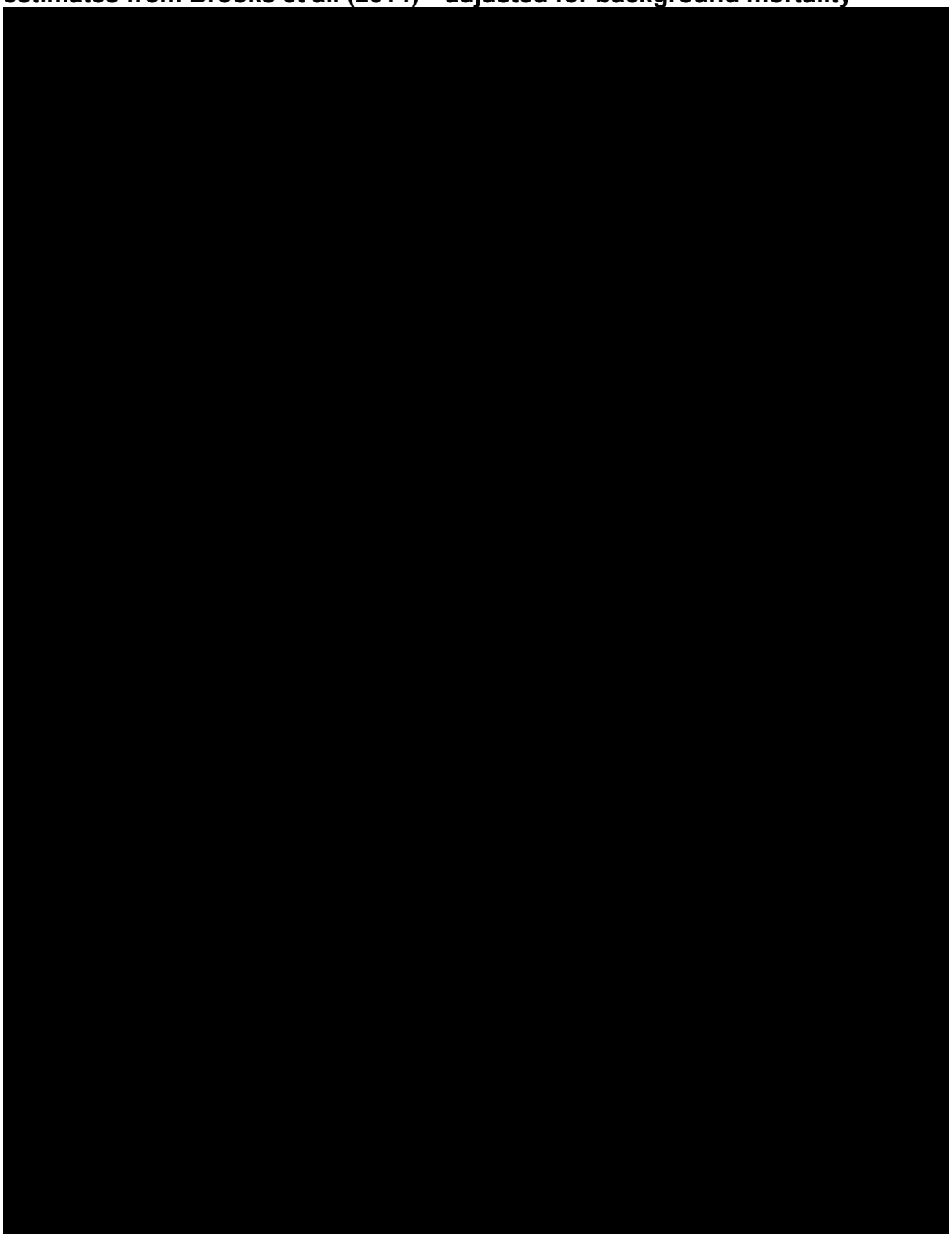
In the Company submission, three scenario analyses looking at using alternative parametric curves were presented. The results from these scenarios show that the Company base case is not only the best statistical fit but is also the most conservative modelling approach. Please see Table 22 for the scenario analysis results following the updates to the model in response to the EAG questions.

Table 22: Updated scenarios - varying parametric curve choices and resultant impact on ICER

	Details of the parametric curves selected	ICER (List price)	ICER (PAS price)
Base case	Best fitting curve: Log-logistic for all health states except walking with assistance [exponential]	£176,617	[redacted]
Scenario 1	2nd best fitting curve overall: Weibull for all health states except walking with assistance (exponential)	[redacted]	[redacted]
Scenario 2	Best fitting curves that do not cross (in order by health state: log-logistic, log-logistic, Weibull, log-logistic, exponential)	[redacted]	[redacted]
Scenario 3	Using expected survival from SMA instead of CP (Oskoui 2007, Zerres 1997)	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; PAS – Patient Access Scheme

Figure 5: Results of the models for survival extrapolations based on survival estimates from Brooks et al. (2014)[65] adjusted for background mortality



**the dotted line represents the available time points in age (years) for which data was available for in the Brooks et al. (2014)[65] study*

Treatment waning

B6. Priority question: Please provide clarification on why the economic model did not consider the treatment effect of eladocagene exuparvovec to decline over time? Please conduct scenario analyses considering a treatment waning effect over time.

Company response:

The Company does not consider it relevant or appropriate to model that the treatment effect of eladocagene exuparvovec declines over time as it is not consistent with the clinical trial evidence and the conclusions reached by the EMA during their regulatory review, which states "[redacted]". The Company has therefore not included a scenario in which treatment effect wanes over time.

It is not appropriate to consider a decline in treatment effect for the following reasons:

- **Clinical evidence demonstrates a durable effect on motor function:** As presented in Tai *et al.,* 2021[5], Figure 4, all patients had an improvement from baseline in PDMS-2 total scores following eladocagene exuparvovec and the effect was sustained throughout the follow-up duration. As shown in the response to Question A10, the cumulative number of patients at each motor milestone increased over time, including beyond the 60-month follow-up time point. All patients treated with eladocagene exuparvovec, including those with follow-up beyond 5 years, have higher PDMS-2 total scores than at baseline, demonstrating the long-term motor function improvement with eladocagene exuparvovec. In addition, as noted in question A21, patients with follow-up beyond the trial duration (including up to 120 months) either improved or maintained their motor milestone attainment over time. It should be noted that it is rare for gene therapies to have up to 10 years of follow-up data at the time of health technology assessment and the duration of follow-up is a strength of the Company evidence submission.

- **The AADC enzyme continues to function in all patients throughout follow-up, indicating sustained effects of gene replacement therapy:** Mean fluorodopa (F-DOPA) positron emission tomography (PET) uptake increases from baseline following eladocagene exuparvovec treatment and the increase is sustained throughout follow-up in all eladocagene exuparvovec studies (Figure 2 in Tai *et al.,* 2021[5] and Table 18, Table 24, Figure 37 in Company submission). PET data at 5 years demonstrate the durability of the gene transduction effect and are consistent with the durability of motor milestone development.

- **The immune response against eladocagene exuparvovec declined over time and had limited impact on efficacy:** In addition to PDMS-2 scores and F-DOPA production being maintained over time, there is limited evidence to suggest that an immune response against eladocagene exuparvovec hinders its long-term efficacy. As noted in Tai *et al.,* 2021[5], anti-AAV immunogenicity indicates an immune response against the gene replacement therapy vector capsid and may compromise therapeutic efficacy. In the eladocagene exuparvovec studies, anti-AAV antibodies peaked at Month 6 and declined by Month 12 (Figure 5 in Tai *et al.,* 2021[5]). Importantly, there was no association with the presence of anti-AAV antibodies and efficacy, as indicated by the durable improvements in F-DOPA production and motor function in all patients (as described above), and anti-AAV antibodies did not cause safety signals. This lack of immunogenicity is because the cells in the putamen are non-dividing, so AAV does not reproduce and infect additional cells, and because the blood-brain barrier minimises antigen presentation and immune system cell trafficking. The lack of immunogenicity further highlights that it is not appropriate to consider treatment waning in the economic model.

Health-related quality of life

B7. Priority question: Company submission Appendix H indicates that the searches for HRQoL studies were limited to studies of patients with AADC deficiency. Please clarify why a review was not conducted to identify HRQoL

data used in proxy diseases to AADC deficiency that provide relevant values to the health state utilities.

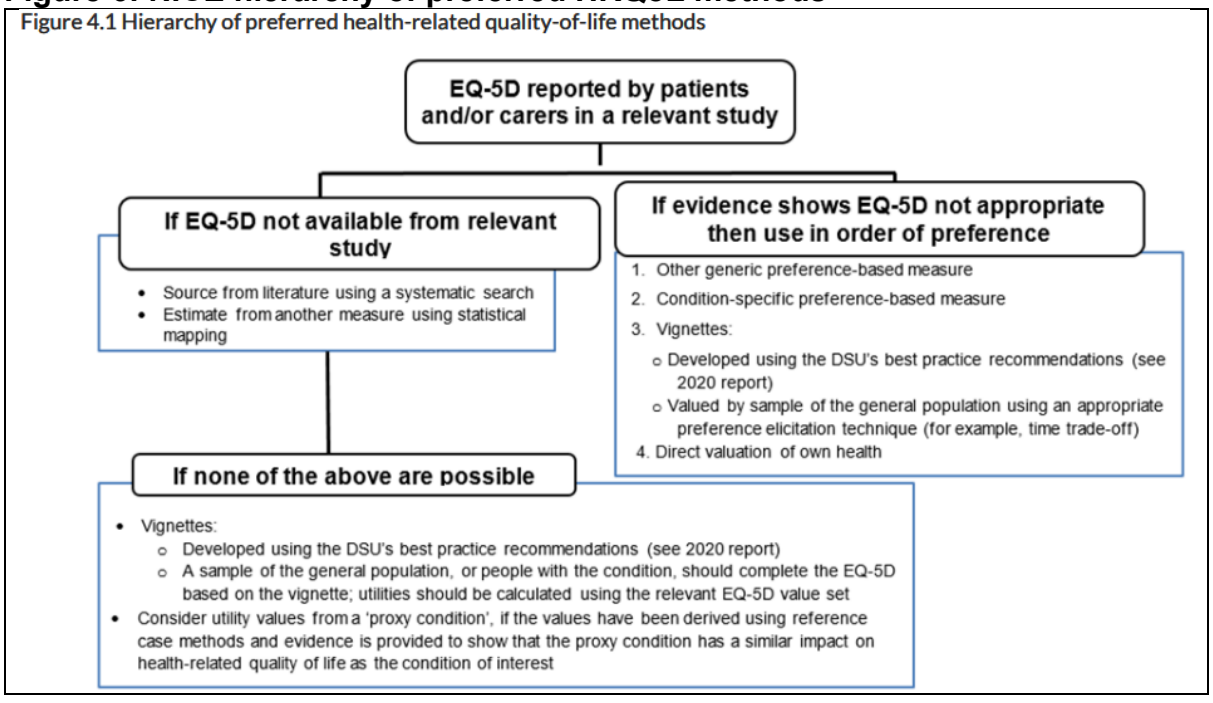
Company response:

The Company systematic literature review successfully identified health state utility values for AADC deficiency (Smith *et al*. 2021[66]) from a vignette study using time-trade off elicitation. Alternative utility values in proxy diseases were therefore not required in the Company submission.

NICE's hierarchy of preferred health-related quality of life methods[67] states that, in conditions where EQ-5D data are not appropriate (as is the case with AADC deficiency due to the young age and cognitive and language impairment of patients), then a preferred alternative approach is to use "vignettes valued by a sample of the general population using an appropriate preference elicitation technique (for example, time trade-off)" (Figure 6). Proxy diseases should only be considered if the values were derived using reference case values and the proxy condition has a similar impact on HRQoL as the condition of interest.

Given that Smith *et al.,* 2021[66] reports utility values from a vignette study in which values were elicited by a UK general population sample, Smith *et al.* 2021[66] is the most appropriate source for the utility values in the Company submission.

Figure 6: NICE hierarchy of preferred HRQoL methods



B8. We have the following questions and request relating to carer quality of life:

(a) Priority question: In the Company submission Executive Summary, it is stated that caregiver quality of life was retrospectively assessed in the eladocagene exuparvovec clinical trials. However, company submission section B.3.4.5.3. states that "quantitative caregiver QoL data were not collected in clinical trials for eladocagene exuparvovec or identified in AADC deficiency patients in the SLR". Please explain this inconsistency.

Company response:

The Company thanks the EAG for pointing out this inconsistency within the Company submission Executive Summary and Company submission section B.3.4.5.3. To confirm, caregiver HRQoL was not prospectively measured in studies AADC-010, AADC-011, or AADC-CU/1601. For further information please refer to question A15.

With regards to the statement given in the Company submission Executive Summary, and as detailed in Tai *et al.,* (2022)[5], the WHO-BREF questionnaire was retrospectively completed by 17 caregivers of patients who received eladocagene exuparvovec. All data collected from the questionnaire are reported in Tai *et al.,* (2022). The data were not included in the economic model.

(b) The economic model presents an option called "QoL study on AADC deficiency caregiver" to choose the caregiver disutility values. Please clarify what QoL caregiver study this option in the model refers to?

Company response:

The "QoL study on AADC deficiency caregiver" option relates to a QoL study conducted by the Company with caregivers of AADC deficiency patients from four different countries (Italy, Portugal, Spain and US). The results of the survey were not considered appropriate for use in the Company base-case or a scenario analysis in the economic model, for the reasons detailed below.

In the caregiver survey, caregivers were asked to fill the EQ-5D-5L questionnaire, a generic QoL preference-based instrument measured on five health dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The

responses from the caregivers were converted to utility values using UK crosswalk value set. The utility values for each caregiver were then compared to the age-matched UK general population utility values, sourced from a study by Szende et al. (2014).[68] The difference between the caregiver utility values and the age-matched general population utility values provided an estimate for the caregiver disutility values. An average was then calculated across the disutility values of all caregivers (0.080).

The results from the analysis were not considered robust enough to be included in the base-case or scenario analyses in the Company economic model due to the limitations of the study. The survey sample size was very small (N=12 initially). This prevents the Company from interpreting the age-matched general population utility values as appropriate counterfactuals. A much larger sample size is needed to reduce the variance in the estimated disutility values and have unbiased and robust results.

The results were also suboptimal because it was not possible to calculate a disutility value for each motor milestone health state due to the small sample size. It was therefore assumed that the average disutility value (0.080) was only applied to the no motor function, full head control, and sitting with support health states. No caregiver disutility was applied for the standing with support and walking with assistance health states. As this is an assumption, this disutility value has major limitations for use in the economic model. The Company considers the caregiver disutility values by motor milestone health state, derived from a previous HST in patients with multiple sclerosis, to be more appropriate for the economic model.

The study is presented in the EQ-5D ISPOR poster by Williams *et al.* (2021)[69] and a follow-up manuscript has been accepted for publication. It should be noted that the analyses described above were based on N=12 caregivers but the accompanying publications included an additional two caregivers (N=14) who were later added to the study.

(c) Please conduct a scenario analysis using the caregiver disutilities from the eladocagene exuparvovec clinical trials.

Company response:

As stated in response to question B8 (a), no caregiver QoL data were obtained from the eladocagene exuparvovec trials. A scenario analysis using caregiver disutilities from the eladocagene exuparvovec trials is therefore not possible.

B9. Company submission, Section B.3.4.5.3, Table 49, details the number of primary caregivers associated with each motor milestone state. Please provide clarification on how the number of caregivers for the health state: walking with assistance (1.2) was obtained.

Company response

There is very limited published data on the number of caregivers associated with looking after patients with AADC deficiency. As such, a total of 1.2 caregivers per patient in the "walking with assistance" health state is an assumption based on clinical expert input that the caregiver burden of AADC deficiency would decrease as patient motor function improves. UK clinical experts have validated both the assumption that the caregiver burden reduces as a patient accrues motor milestones and the assumption that patients in the "walking with assistance" health state would require 1.2 caregivers.[70] Further information is provided below on the sources and assumptions underpinning the caregiver numbers in the model.

In the economic model, the caregiver number for patients in the worst motor milestone health state (No-motor function) is 2.2, based on a value accepted by NICE in a previous HST for risdiplam in SMA.[71] From 2.2 caregivers in the worst health state, the model assumes that caregiver numbers decrease linearly to 1.2 caregivers in the best health state (Table 23). The Company assumed a value of 1.2 caregivers for the best health state as it is 1 caregiver difference from the 2.2 caregivers in the worst health state. It is a conservative assumption as opposed to using 1 caregiver in the best health state.

The Company considers it to be appropriate to assume that caregiver numbers decrease as a patient accrues motor milestones. The approach to use differing caregiver numbers for different health states is in line with that used for nusinersen in SMA (3 caregivers in the worst health state, 2 in the best health state).[72]

In addition, UK clinicians consulted as part of this AADC deficiency appraisal confirmed that 2.2 caregivers is appropriate for patients with no motor function, stating

that AADC deficiency patients with more severe symptoms would require more care than those with less severe symptoms.[70] Upon further discussion with a UK clinical expert throughout the EAG clarification process, the expert agreed that caring for an individual would be easier if they were an ambulant patient and suggested around 1 caregiver per patient in that health state. The clinician suggested that around 2 caregivers would be needed for patients who were in a non-ambulant health state, as more help would be needed for moving the patient.

Table 23: Number of primary caregivers associated with each motor milestone state as used in the base-case CEA

AADC deficiency motor milestone health state	Number of primary caregivers*
No-motor function	2.20
Full-head control	1.95**
Sitting unassisted	1.70**
Standing with support	1.45**
Walking with assistance	1.20

**Based on UK clinician input[70] and TA755 for treatment with for risdiplam in SMA[71]*
***The Company would like to clarify that Table 49 in the Company submission Section B.3.4.5.3 contains incorrect values, but the values inputted into the model were correct and align to those presented above*
Abbreviations: AADC – aromatic L-amino decarboxylase; SMA – spinal muscular atrophy; TA – technology appraisal

Adverse events

B10. Please provide the rationale for including moderate-to-severe TEAEs affecting ≥20% of patients within the first 12 months of follow-up in the economic model (company submission, Section B.3.2.2.12, Table 40) – why was the ≥20% cut-off chosen?

Company response:

A conservative approach was taken in the CEA whereby treatment-emergent AEs were considered as opposed to treatment-related AEs. Moderate-to-severe TEAEs affecting ≥20% of patients within the first 12 months of follow-up was chosen for the economic model due to the very small number of patients included in the trial population (N=28). Using a ≥5% cut-off (as is typical across larger-trial cohort modelling and as requested by the EAG in B2) would mean that only two patients would need to experience an AE for it to be considered a relevant TEAE. The Company considers 2 patients to be too low as a threshold for including in the economic model. The ≥20% threshold was therefore considered more appropriate as

it is more likely to be reflective of a true TEAE associated with treatment with eladocagene exuparvovec.

To address the EAGs query over the threshold (and in response to question B2), the Company has developed a scenario analysis modelling moderate-to-severe TEAEs affecting ≥5% of patients within the first 12 months of follow-up. This scenario can be explored using a simple switch within the safety section of the economic model. The impact on the ICER of changing the threshold from ≥20% to ≥5% is negligible.

Costs

B11 Priority question: Company submission, Section 3.5.2.1, Table 57, presents the proportion of patients treated with each treatment category in the best supportive care basket per motor milestone. Please clarify how the patient proportions were obtained. Please provide the source that supported the distribution of symptomatic treatments by motor milestone health state.

Company response:

The proportion of patients treated with each treatment category in the BSC basket was based on the results from the survey conducted with clinical experts with experience managing AADC in Europe. This is the same study that is presented in Saberian *et al.* (2021).[25] It should be noted that the survey data related to the distribution of BSC treatments by motor milestone health state was not published in Saberian *et al.* (2021).

B12. Company submission, Section B.3.5.1.2.3, Table 55, states that the costs for Upper Limb Splints, Lower Limb Splints, and Verticalizers are assumed. Please provide a rationale for these cost assumptions.

Company response

The costs for Upper Limb Splints, Lower Limb Splints, and Verticalizers were assumption values in Table 55 of the Company submission Section B.3.5.1.2.3. The Company has now sourced costs for these pieces of equipment (Table 24).

The costs for Upper Limb Splints and Lower Limb Splints were sourced based on UK clinical expert input. The cost of Verticalizers, also referred to as standing frames, was sourced from a UK study around the use of standing frames for children with cerebral

palsy (Goodwin *et al.* (2017)).[73] The cost in Goodwin *et al.* (2017) was inflated to 2019/2020 using the inflation indices from the PSSRU 2020[74] report. The model uses the upper range of costs for each piece of equipment.

The revised base-case results (comprising the combined updates of B12, B13, B14, B19, B20 and B21 are presented in B21 (Table 29 and Table 30).

Table 24: Unit costs for Upper Limb Splints, Lower Limb Splints and Verticalizers

Resource use	Cost	Source
Upper limb splints	£120.00	Clinician input
Lower limb splints	£350.00	Clinician input
Verticalizers	£2,668.60	Goodwin *et al.* (2017), inflated to 2019/2020 year using PSSRU infaltion indices

Abbreviations: PSSRU – Personal Social Services Research Unit

B13. In company submission, Section B.3.5.1.2.1, Table 52, the company submission states that the dosage for pramipexole is 0.5mg/kg/day; however, the source, Wassenberg et al. (2017), states that the dosage should start from 0.005-0.01mg/kg/day and increases to a maximum for 0.075/mg/kg/day or 3.3mg/day. Please justify the significant dosage increase or update the model calculations with the appropriate dosage as stated in the source.

Company response:

The Company thanks the EAG for pointing this out. The 0.5mg/kg/day dosage of pramipexole was an error. The dosage of pramipexole in the model has now been changed 3.3mg/day within the calculations, aligning with Wassenberg *et al.,* (2017).[6]

The revised base-case results (comprising the combined updates of B12, B13, B14, B19, B20, and B21) are presented in the response to B21 (Table 29 and Table 30).

B14. In company submission, Section B.3.5.1.2.1, Table 53, which details the best supportive care treatment acquisition costs, "Ensure Plus Advance" has been included as a dietary supplement. However, in the BNF and literature, this dietary supplement is not recommended for children, and instead is designed for patients aged 65 years and over. Please provide the rationale for including this in the acquisition cost estimation.

Company response:

The company would like to thank the EAG for pointing out that “Ensure Plus Advance” is not recommended for children. The Company agrees that the BNF only recommends “Ensure Plus Advance” in patients over the age of 65 years. Given the young age of the AADC deficiency population included in the CEA, coupled with the fact dietary supplements are not included in the BSC treatments noted in Wassenberg *et al.* (2017) and Brun *et al.* (2010), the Company considers it appropriate to remove Ensure Plus Advance from the economic model.

The impact of removing Ensure Plus Advance from the economic model is negligible as it is very low cost (£2.20) and is used in a similar proportion of patients across the five motor milestone health states, meaning that removing it from the model has a similarly small impact on both the BSC and eladocagene exuparvovec arms. The impact on the ICER for eladocagene exuparvovec versus BSC is therefore negligible.

The revised base-case results (comprising the combined updates of B12, B13, B14, B19, B20, B21) are presented in B21 (Table 29 and Table 30).

B15. The annual number of visits/procedures by motor milestone health state has been mapped from Saberian et al. (2021) (company submission, Section B.3.5.2.2, Table 58, Table 59, and Table 60). The three motor milestone health states in Saberian et al. (2021) are (1) No-motor function or full-head control only; (2) Sitting unassisted or standing with assistance; and, (3) Walking assisted or unassisted. The EAG have surmised that the company have mapped data from (1) to the no-motor function and full-head control motor milestones in the company submission, and mapped data from (3) to the standing with support and walking with assistance motor milestones in the company submission. It appears that the data for the sitting unassisted motor milestone has been calculated as a median point between the no-motor function and walking with assistance motor milestones. We have the following requests related to this:

- **(a) Please provide a rationale as to why the data from ‘Walking assisted or unassisted motor milestone’ in Saberian et al. have been used for standing with support motor milestone in the company submission,**

when Saberian et al. has data for the standing with assistance motor milestone.

Company response:

The EAG is correct that the three motor milestone health states in Saberian *et al.* (2021)[25] are (1) No-motor function or full-head control (N=8 patients); (2) Sitting unassisted or standing with assistance (N=2 patients); (3) Walking assisted or unassisted (N=8 patients). These health states are partially aligned to the Company economic model health states, so a mapping exercise was needed to determine the appropriate Saberian *et al.* resource use values to use in the Company submission. The EAG is correct in their understanding of how the Saberian *et al.* (2021) values have been mapped to the health states in the Company submission. Please see Table 25 for a summary of the resource use mapping from Saberian *et al.* (2021).

Table 25: Mapping of Saberian et al. resource use values to Company submission health states

Company submission health state	Resource use value mapping from Saberian et al. (2021)
No-motor function	Resource use values from Saberian et al "no-motor function or full-head control" health state
Full-head control	
Sitting unsupported	Median point between Saberian et al "no-motor function or full-head control" and "walking assisted or unassisted" values
Standing with support	Resource use values from Saberian et al "walking assisted or unassisted" health state
Walking with assistance	

When conducting the mapping, the Company decided that the resource use values for the "sitting unassisted or standing with assistance" health state from Saberian *et al.* (2021) were not appropriate for use due to the small sample size (N=2). The small sample size led to resource use values that were inconsistent and counterintuitive compared with resource use in the other health states.

To account for the inconsistent results, the Company assumed that resource use in the "standing with support" health state was equivalent to the values for the "walking with assistance" health state (i.e. the resource use for "standing with support" in the Company submission is assumed to be the same as that for "walking with assistance", and the resource usage for patients who have reached the "sitting unassisted" health state is assumed to be the average of the "no-motor function" or "full-head control"

resource usage and the “walking with assistance” resource usage from Saberian *et al.* (2021).

The resource use values in the economic model were validated in a clinical expert advisory board (July 2021).[12]

(b) Please provide a rationale as to why data for ‘sitting unassisted motor milestone’ in the company submission is calculated as a median, when Saberian et al. has data for the corresponding motor milestone.

Company response:

As mentioned in response to question B15a, the small sample size (N=2) in the “sitting unassisted or standing with support” health state in Saberian *et al.* (2021)[25] led to results that were inconsistent and counterintuitive compared with the resource use in the other health states. The Company therefore decided not to use the resource use values for the Saberian *et al.* “sitting unassisted or standing with support” health state.

To account for the inconsistent results, the Company assumed that the resource use for the economic model “sitting unassisted health state” was an average of the Saberian *et al.* value for the resource use in the “no-motor function or full-head control” health state and the “walking assisted or unassisted” health state (see Table 25).

The resource use values in the economic model were validated in a clinical expert advisory board (July 2021),[12] during which where the clinical experts agreed that patients in the “sitting” health state would require more resources than patients who can walk.

(c) Many of the calculations from Saberian et al. to the company submission tables are incorrect, as indicated in the following table. Please correct the values in the model.

Type	CS/Model	Source
General Practitioner	2.13 (no-motor function and full head control) 1.79 (sitting unassisted) 1.45 (standing with support and walking with assistance)	2.10 (no-motor function and full head control) 1.77 (sitting unassisted) 1.44 (standing with support and walking with assistance)

Neurologist	2.50 (no-motor function and full head control) 2.08 (sitting unassisted) 1.65 (standing with support and walking with assistance)	2.54 (no-motor function and full head control) 2.11 (sitting unassisted) 1.68 (standing with support and walking with assistance)
Occupational therapy	39.25 (no-motor function and full head control)	39.26 (no-motor function and full head control)
Physiotherapist	84.80 (no-motor function and full head control) 55.72 (sitting unassisted)	84.83 (no-motor function and full head control) 55.74 (sitting unassisted)
Psychiatrist	3.33 (sitting unassisted) 6.15 (standing with support and walking with assistance)	3.34 (sitting unassisted) 6.18 (standing with support and walking with assistance)
Speech therapist	16.31 (no-motor function and full head control)	16.3 (no-motor function and full head control)
Hospitalisation	1.88 (no-motor function and full head control) 1.39 (sitting unassisted)	1.84 (no-motor function and full head control) 1.37 (sitting unassisted)
Blood test	0.88 (no-motor function and full head control) 0.87 (sitting unassisted) 1.00 (standing with support and walking with assistance)	0.90 (no-motor function and full head control) 0.96 (sitting unassisted) 1.02 (standing with support and walking with assistance)
Coagulation test	0.73 (sitting unassisted)	0.83 (sitting unassisted)
Electro-encephalography	0.45 (sitting unassisted)	0.43 (sitting unassisted)
Folic acid dosage in CSF	0.03 (sitting unassisted)	0.015 (sitting unassisted)
Iron dosage	0.88 (no-motor function and full head control) 0.87 (sitting unassisted) 1.00 (standing with support and walking with assistance)	0.90 (no-motor function and full head control) 0.96 (sitting unassisted) 1.02 (standing with support and walking with assistance)
Lumbar puncture	0.03 (no-motor function and full head control) 0.04 (sitting unassisted)	0.00 (no-motor function and full head control) 0.015 (sitting unassisted)
MRI	0.35 (no-motor function and full head control) 0.26 (sitting unassisted) 0.15 (standing with support and walking with assistance)	0.34 (no-motor function and full head control) 0.25 (sitting unassisted) 0.16 (standing with support and walking with assistance)
ECG	0.88 (sitting unassisted) 1.30 (standing with support and walking with assistance)	1.04 (sitting unassisted) 1.33 (standing with support and walking with assistance)
Prolactin dosage	0.97 (sitting unassisted) 1.15 (standing with support and walking with assistance)	1.06 (sitting unassisted) 1.12 (standing with support and walking with assistance)
Urine test	0.81 (sitting unassisted) 1.00 (standing with support and walking with assistance)	0.89 (sitting unassisted) 1.02 (standing with support and walking with assistance)
X-ray (spine)	0.23 (sitting unassisted) 0.15 (standing with support and walking with assistance)	0.21 (sitting unassisted) 0.16 (standing with support and walking with assistance)

Verticalizers	0.23 (no-motor function and full head control) 0.11 (sitting unassisted)	0.25 (no-motor function and full head control) 0.13 (sitting unassisted)

Company response:

The Company agrees that the values in the economic model do not align with those reported in Saberian *et al.* (2021)[25] but we do not believe that the model values are incorrect or need updating.

In calculating the values for the model and the corresponding tables in the Company submission, the Company used the raw data underlying the Saberian *et al.* (2021) study, which was presented to more decimal places than the values provided in the poster. Therefore, the values in the Company submission and economic model are estimated to a higher degree of accuracy, meaning that the values in the current model do not need to be updated.

Economic model

B16. Priority question: In Sheet 'Survival_calc'!D72:F82, the rate and shape estimates for the Gompertz parametric model to extrapolate survival curves are assumed to be same for all the health states (that is, the parameters for full-head control, sitting unassisted, standing with support and walking with assistance are assumed to be same as those for no-motor function). Please explain the rationale for this assumption.

Company response:

The Company would like to clarify that the Gompertz parametric model parameters described in question B16 above were left in the economic model during an quality checking exercise. As detailed in the Company response to question B5, the Gompertz parametric model does not converge for the full-head control, sitting unassisted and standing with support motor milestones. The values in 'Survival_calc'!D72:F82 were inputted for a quality check to see if the Gompertz distribution was implemented correctly in the economic model.

To avoid confusion, the Company has now removed the values in 'Survival_calc'!D72:F82 from the model.

B17. Priority question: In Sheet 'Survival_calc'!D92:F102 and D132:F142, please explain why the parameters for the lognormal and gamma distributions are missing.

Company response:

The Company thanks the EAG for pointing this out. As detailed in the Company response to question B5, the lognormal and gamma parametric models do not converge for the full-head control, sitting unassisted, standing with support, and walking with assistance motor milestones. The accompanying parameters are therefore excluded from the economic model for those motor milestones.

B18. Priority question: In Sheet 'Input conversion'B309:AC319, the model presents three different options to model motor milestones directly from the observed data, as follows:

i) **Option 1: % based on original sample**

ii) **Option 2: patient distribution (distribution per follow-up)**

iii) **Option 3: patient distribution based on clinical trial data (last observation carried forward)**

Please clarify:

(a) what the difference is between each of these three options.

Company response:

The three different options are defined as follows:

Option 1: % based on original sample: These are the observed clinical trial data, not taking into account missing data. By not considering missing data, the proportion of patients across the motor milestones does not sum to 100% for the later time points (Table 26). This essentially causes patients with missing data to be lost at the end of their follow-up, meaning they are excluded from the model and accrue no further life years, QALYs, or costs. As can be seen in Table 26, a considerable proportion of patients would be lost from the model using this approach.

Table 26: Observed proportion of patients at different time points up to and including 60 months in the eladocagene exuparvovec studies (N=28)

Time (months)	Patients with motor milestone data at each time point, % (N)
0 (Baseline)	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

Option 2: patient distribution (distribution per follow-up): These are the observed clinical trial data but take into account missing data. By considering missing data, the proportion of patients in each motor milestone at each time point is the proportion of patients in that motor milestone out of the total number of patients with data at that time point. This means percentages total 100% for all time points.

Option 3: patient distribution based on clinical trial data (last observation carried forward): These are the observed clinical trial data, with a patient's last observation carried forward through to the five-year follow-up time point for those patients with less than five years of follow-up data.

(b) why the company have decided to use option 3 in their scenario analysis modelling motor milestones directly from the trials rather than option 1 (ICER of [redacted] per QALY) or 2 (ICER of [redacted] per QALY).

Company response:

The Company does not consider Option 1 to be appropriate as it did not account for patients with missing data at the longer follow-up time points (see Table 26). This meant that the economic model analyses at later time points did not include the whole trial population and assumed that all patients exited the model at the end of their follow-up. This adds considerable bias and error to the cohort results.

Option 3 (using last observation carried forward for patients without longer-term follow-up data) was chosen over Option 2 following discussions with clinical experts, who stated that patients would at least maintain their last achieved motor milestone over time. The Company therefore conservatively assumed that patients would maintain their last achieved motor milestone attainment over time (rather than assuming an improvement in motor milestone, which is observed in some patients with longer follow-up). Furthermore, due to the low sample size of the trial population (N=28), using Option 2 would mean that each patient with data for the later time points carries a considerable amount of weight in the analysis, leading to potentially unreliable motor milestone distributions.

B19. Priority question: In Sheet! 'Cost_calcs'!O17:S17, the costs of follow-up visits with specialists includes one-off costs not directly related to specialist visits. However, these one-off costs were already included in the drug acquisition costs as part of the pre- and post-operative costs (see model 'Cost_calcs'!H16). Please clarify the reason for the inclusion of these one-off costs as part of the follow-up visit costs, as this is not explained in the company submission.

Company response:

The Company thanks the EAG for pointing this out. The inclusion of the one-off administration and pre-/post- operative costs as part of the follow-up visits within the specialists' costs is an error within the model. The model has now been updated to include the one-off administration and pre-/post- operative costs as part of the drug acquisition costs only.

The revised base-case results (comprising the combined updates of B14, B19, B20, and B21) are presented in B21 (Table 29 and Table 30).

Inconsistencies between the company submission, economic model and sources

B20. Priority question: The following values provided in the company submission /model do not match the values provided in the source. Please explain the inconsistencies.

	CS/Model	Source values (obtained by the ERG)	Notes
Health state utility			
No-motor function	SE 0.0096	SE 0.3429	Smith et al. (2021) (ref 28)
Full-head control	SE 0.0091	SE 0.3255	Smith et al. (2021) (ref 28)
Sitting unassisted	SE 0.0087	SE 0.3099	Smith et al. (2021) (ref 28)
Standing with support	SE 0.0086	SE 0.3073	Smith et al. (2021) (ref 28)
Walking with assistance	SE 0.0086	SE 0.3052	Smith et al. (2021) (ref 28)
Adverse events – disutilities			
Gastroenteritis	0.075	0.0725	Sullivan et al. (2011) (ref 126). Value in Table 50 matches source; value in Table 46 and in model does not match source.
Caregiver disutilities			
No-motor function	SE 0.02	SE 0.075	Acaster et al. (2013) (ref 29)
Full-head control	SE 0.02	SE 0.075	Acaster et al. (2013) (ref 29)
Sitting unassisted	SE 0.006	SE 0.038	Acaster et al. (2013) (ref 29)
Standing with support	SE 0.006	SE 0.038	Acaster et al. (2013) (ref 29)
Bereavement disutility	0.037	0.039	Song et al. (2010) (ref 118)
Medical costs			
Otolaryngologist	£130.63	£129.80	NSRC 19/20
Pulmonologist	£218.23	£227.54	NSRC 19/20
ECG	£49.00	£106.77	NSRC 19/20

Company response:

The Company would like to thank the EAG for pointing out the potential inconsistencies and errors in the model values in the table above.

Regarding the health state utility values, the inconsistencies between the standard error (SE) values provided in the CEA base-case can be explained. The values sourced from the Smith *et al.* (2021)[66] publication and obtained by the EAG are values for the standard deviation (SD) of the utility parameters. As the CEA utilises SE as a measure of variance consistently within the model, the Smith *et al.* (2021)[66] SD values were used to calculate the SE values ($SE = \frac{SD}{\sqrt{N}}$, where N is the sample size of 1,268) used within the model. For example, the no-motor function health state utility value SD

in Smith *et al.*[66] was 0.3429 and was converted to SE as follows: $\frac{0.3429}{\sqrt{1268}} = 0.0096$ (to 2 decimal places).

Regarding caregiver disutility, the SE values were originally calculated by the Company by multiplying the disutility parameters by a 20% variance. However, as the EAG have pointed out, the Acaster *et al.* (2013) publication, reports the SE values for the caregiver disutilities and therefore these published values have now been updated and implemented within the CEA.

The remainder of the parameters highlighted in the table provided by the EAG as part of B20 have now also been updated in the model to correct the erroneous values. The model values now align with the appropriate sources and are consistent with the values identified by the EAG. Table 27 presents the updated values now used within the CEA.

The revised base-case results (comprising the combined updates of B14, B19, B20, and B21) are presented in B21 (Table 29 and Table 30).

Table 27: Updated values implemented in the cost-effectiveness analysis based on Question B20

	Updated value	**Reference**
Adverse events – disutilities		
Gastroenteritis	0.0725	Sullivan et al. (2011). Value is now consistent with Table 46, Table 50 and the model within the submission.
Caregiver disutilities		
No-motor function	SE 0.075	Acaster *et al.* (2013)
Full-head control	SE 0.075	Acaster *et al.* (2013)
Sitting unassisted	SE 0.038	Acaster *et al.* (2013)
Standing with support	SE 0.038	Acaster *et al.* (2013)
Bereavement disutility	0.039	Song *et al.* (2010)
Medical costs		
Otolaryngologist	£129.80	National Schedule of Reference Costs 2019/20: paediatric ENT, non-admitted F2F follow-up visit (WF01A)

Pulmonologist	£227.54	National Schedule of Reference Costs 2019/20: paediatric respiratory medicine, non-admitted F2F follow-up visit (WF01A)
ECG	£106.77	National Schedule of Reference Costs 2019/20: Electrocardiogram Monitoring or Stress Testing (EY51Z)

Abbreviations: ECG, electrocardiogram; ENT, Ear, nose, and throat; F2F, face-to-face; SE, standard error

B21. Priority question: The ERG were unable to locate the following medication prices in the BNF as used by the company in their cost calculations. Please provide the appropriate sources (including web links).

Medication costs	Company submission/Model	Notes
Pramipexole	180mg, £13.92	Maximum strength of medication available is 3.15mg, not 180mg. No strength of medication in BNF matching cost in CS/model.
Ropinirole	£21.51	No medication in BNF matching cost in CS/model.
Bromocriptine	Pack of 100, 10mg	Maximum pack size is 30 tablets. Maximum medication strength is 2.5mg.
Tranylcypromine	£429.61	No medication in BNF matches cost in CS/model.
Trihexyphenidyl hydrochloride	£5.51	No medication in BNF matches cost in CS/model.
Diazepam	£1.06	No medication in BNF matches cost in CS/model.
Melatonin	£19.75	No medication in BNF matches cost in CS/model.
Folic acid	£1.03	No medication in BNF matches cost in CS/model.

Company response:

The company would like to thank the EAG for pointing out the erroneous values in the table above. The values have now been updated within the model to align with the appropriate BNF source. Table 28 below presents the updated values used in the updated economic model.

Table 28: Updated values implemented in the CEA based on Question B21

Medication costs	Updated value	Reference
Pramipexole	Pack of 100, 0.18mg; £6.22	BNF (2021)
Ropinirole	£32.42	BNF (2021)

Bromocriptine	Pack of 30, 30mg	BNF (2021)
Tranylcypromine	£488.49	BNF (2021)
Trihexyphenidyl hydrochloride	£3.97	BNF (2021)
Diazepam	£0.87	BNF (2021)
Melatonin	£19.81	BNF (2021)
Folic acid	£0.91	BNF (2021)

Table 29 and Table 30 present the revised economic base-case results, considering the updated costs from question B12, the updated dosage from question B13, the removal of dietary supplement from question B14, the edit from question B19 and the updates to parameters and costs highlighted in question B20 and B21.

Table 29: Revised base case ICER (list price) following updates to address clarification questions B12, B13, B14, B19, B20, B21

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,617

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; LYG – life year gain; QALY – quality-adjusted life year

Table 30: Revised base case ICER (PAS price) following updates to address clarification questions B12, B13, B14, B19, B20, B21

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; LYG – life year gain; PAS – patient access scheme; QALY – quality-adjusted life year

Section C: Textual clarification and additional points

C1. Company submission, Section B.2.9.5, states: "In all analyses, the effective sample size reduces substantially, with less than 5 patients available for analysis when matching by (a) sex, race, mutation category, and age at diagnosis, or (b) sex and race." Company submission, Table 28, states the effective sample size when matching using sex and race is 8.08. Is the textual statement of "less than 5 patients" an error?

Company response:

The Company can confirm that this was a textual error and should have read "less than 10 patients" instead of "less than 5 patients".

C2. Company submission, Section B.2.9.7, states "the lack of heterogeneity between BSC options utilised across individual patients in clinical practice limited the feasibility of conducting an adjusted ITC". Please clarify:

a) If this means that in clinical practice in England, best supportive care treatment is homogenous across patients?

Company response:

The Company thank the EAG for clarifying this textual error. We can confirm that this should be amended to "high heterogeneity", meaning that BSC treatments use varies substantially in patients with AADC in clinical practice in England and Europe.

b) why this limited the feasibility of carrying out the adjusted ITC?

Company response:

The Company confirm that the amended sentence should be "the high heterogeneity between BSC options utilised across individual patients in clinical practice limited the feasibility of conducting an adjusted ITC". High heterogeneity limits the feasibility of carrying out an adjusted ITC. Homogeneity between treatment options is an important assumption when carrying out adjusted ITCs, as treatment comparisons are often based on similarity and consistency assumptions.[75] Therefore, heterogeneity in studies may limit the validity of the results of an ITC.[76]

C3. Company submission, Section B.2.2, states that the CSR for the AADC-011 study "is currently being updated with additional analyses" and that the "final version was not available at the time of the NICE submission deadline". Is the updated version now available? If so, please supply a copy.

Company response:
The final CSR for AADC-011 is not yet available. The Company is therefore currently unable to provide a copy.

C4. Please provide the statistical analysis plan (SAP) for AADC-CU/1601.

Company response:
The Company has included a PDF file containing the SAP for AADC-CU/1601 in the reference pack sent alongside these responses.

C5. Please provide the study protocols for all 3 studies (AADC-010, AADC-011, and AADC-CU/1601).

Company response:
The Company has provided PDF files containing the SAPs and protocols for all three studies.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	The AADC Research Trust

3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The AADC Research Trust is an international non-profit patient organisation, representing children and young adults suffering with the ultra-rare neurotransmitter disorder, Aromatic Amino Acid Decarboxylase deficiency (AADCd). The AADC Research Trust is an entirely patient centric organisation, where safeguarding our community is paramount. We are funded by public donations, community fundraising and grants. We are connected with over 80% of the worlds AADCd patient population, spanning thirty countries. The Trust has fostered and collaborated with a global network of medical and scientific experts for over 15 years. We are at the forefront of critical disease research and have been the architect of major projects including the largest natural history study, the publication of the Consensus Guidelines for the diagnosis and treatment of l-amino acid decarboxylase (AADC) deficiency, the implementation 3-O-methyl dopa (3-OMD) as a unique biomarker, induced pluripotent stem cells research (iSPC), a rigorous study into genetic variables, and many more. We have been a significant driver, for over a decade, in the evolution of pioneering gene therapy surgeries and provided a platform to project the data via four international conferences We are dedicated to helping children and their families affected by AADCd, navigate the highly complex, challenging and often lonely rare disease journey.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered from an online AADC Insight survey issued via social media channels and direct mailing. This survey was designed by The AADC Research Trust and Metabolic Support UK . The survey was designed to understand the impact of living with AADCd and patients views on current treatment options including Eladocagene exuparvovec. The survey received a total of 8 responses and details of our findings have been included in this submission. In conjunction with this The ADDC Research Trust and Metabolic Support UK also hosted a series of recorded insight interviews with patients and caregivers living with AADCd. The interviews provided the opportunity to gather further insights regarding the impact of the condition, gather case studies and qualitative views on current and future treatment options. We interviewed 4 participants and will shortly publish our findings in a collaborative AADC Insight report.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Aromatic L-amino acid decarboxylase deficiency is a genetically inherited neurometabolic disorder which affects the brains ability to produce neurotransmitters; dopamine and serotonin. Typically, AADCd presents early in life and symptom severity varies based on the individual patient. AADCd is an ultra-rare and debilitating disorder. Patients living with AADCd experience the following symptoms. 1. Oculogyric crises 2. Sustained muscle contraction (dystonia) 3. Abnormal posture 4. Involuntary movements (dyskinesia) 5. Tremors 6. Droopy eyelids 7. Temperature instability 8. Low blood pressure (hypotension) 9. Low blood sugar (hypoglycemia) 10. Seizures 11. Insomnia 12. Gastrointestinal problems 13. Developmental delays 14. Lack of muscle tone (hypotonia) and /or too much muscle tone (hypertonia) 15. Movement disorders 16. Excessive sweating (hyperhidrosis) 17. Nasal congestion, drooling, reflux, and choking 18. Sensitivity to noise and light

19. Anxiety, depression, irritability and excessive crying
20. Slow heart rate (bradyarrhythmia)

The physical and psychosocial impact of living with AADCd is significant. Over 50% of survey respondents rated their child's quality of life as poor. A majority of the respondents had experienced all of the symptoms listed above, with varying degrees of severity between mild and severe. We asked respondents to indicate the symptoms that have the most impact on quality of life and the results were as follows; lack of muscle tone (hypotonia), development delays, movement disorders (dyskiesia), excessive sweating (hyperhidrosis), abnormal posture, insomnia, gastrointestinal problems and nasal congestion.

The symptoms and manifestations of AADCd also impact a patient's ability to carry out daily activities such as heavy lifting, walking at a fast pace, carrying groceries, completing chores, walking uphill, climbing stairs, bending, lifting, walking short distances, eating, dressing independently and bathing. We asked patients and parent/carers to indicate which of their daily activities have been most impacted as a result of AADCd. The top three activities were; walking at a moderate/fast pace, bending or lifting. A large majority (75%) of respondents indicated that their child uses mobility aids and assistive cognitive aids to help them manage daily activities. A majority of respondents have also made physical adaptations to their home to assist their child's daily activities and accessibility.

People living with AADCd are not only dependent on assistive equipment and modifications but also the support of external services. 50% of respondents indicated they receive care and support from social services and 37% receive support from a homecare provider. Despite the additional support to manage the condition at home, half of the survey respondents indicated their child had been admitted to hospital within the last 12 months. Over 50% of respondents indicated they do not find the condition easy to manage.

The psychological and social impact of AADCd is also significant. AADCd does not just affect the immediate family but also the wider family network, including friends and peers. Patients and carers find it difficult to socialise with others, often feel anxious or worried about their future, find it difficult to talk about their feelings, feel isolated and alone, often feel frustrated and unable to cope or seek help from family, friends and professionals for their mental health.

Case study 1 (Anonymised)

Parent/carer X has a child living with AADCd, Patient Y. Patient Y was initially misdiagnosed with multiple forms of epilepsy. Patient Y's symptoms were short cyclical periods of oculogyric crisis, dystonia and hypertonia. Patient Y was initially prescribed diazepam which worsened their symptoms and L-Dopa which did not improve symptoms. Parent/carer X conducted independent research and following an observation by a specialist and a lumbar puncture test, Patient Y was diagnosed with AADCd.

Case study 2 (Anonymised)

Parent/carer A has a child living with AADCd, Patient B. After noticing developmental delays alongside physical symptoms such as dystonia, the parents of Patient B took videos of these episodes and visited over 10 doctors in order to find a diagnosis that went beyond just having seizures. After 2 years, a genetic test confirmed a diagnosis of AADCd.

The doctor that diagnosed the patient had not previously been aware of AADCd. The patient's parents describe the shock when reflecting on the journey to diagnosis as an 'incredibly stressful time'. The mother of the patient has had to give up work in order to care for the patient and as a family, they avoid leaving their home given it would be so uncomfortable and impractical to do so, resulting in feelings of isolation from society.

Case study 3 (anonymised)

Parent/carer C has a child living with AADC, Patient D. Following a multitude of physical symptoms including a failure to thrive and stiffness, an EEG was performed to confirm whether symptoms related to seizures. Following different examinations including blood tests and other diagnostic procedures, an AADCd diagnosis was confirmed.

Following diagnosis Patient D developed symptoms including having no energy, poor sleep, low blood sugar, low weight, which resulted in multiple trips to A&E. As a result of adjusting to the difficult symptoms, continued uncertainty, and feeling of isolation, Parent C experienced a deterioration of their mental health.

Case study 4 (anonymised)

Parent/carer E has a child living with AADCd, patient F. After a difficult birth and needing constant comfort alongside what was eventually confirmed to be oculogyric crises lasting up to 8 hours, patient F was assumed by their local hospital and health visitors to have reflux. Following their own research, and a hospitalisation of Patient F elsewhere, AADCd was considered. A lumbar puncture eventually confirmed a diagnosis of AADCd.

The family have had to stop going out together and have had to adapt life around Patient F and their complex regime. Patient F requires multiple and differing medications 4 x daily and as they enter adolescence, parent E said the management of treatment care is becoming more and more challenging.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most patients manage their condition via prescribed medications such as Vitamin B-6, dopamine receptor agonists (for example, bromocriptine, rotigotine), monoamine oxidase inhibitors and melatonin. A majority of patients rely on a strict dietary regime and sleep schedule to manage their condition. In addition to prescribed medicines, patients also rely on other treatments such as physiotherapy and occupational therapy to manage their condition. 25% of parent/caregivers who took part in our survey, indicated that their child is also in receipt of speech and behavioural therapy to help them manage the condition. One parent/caregiver we interviewed described the current therapy such as physiotherapy and swim therapy as working "*tremendously*" for their child. Stating that despite the slow progression, their child has demonstrated marked improvement in mobility development and being able to form sentences as a result of speech therapy. We asked our interviewees and survey respondents what the other advantages of the current treatment and care options were. Other advantages include improved sleep and reduced severity of dystonia, receiving support from an attentive team, seeing a variety of specialists and a reduction in convulsions. However, despite the advantages, participants indicated there are significantly more drawbacks in relation to current treatment and care options. One respondent stated "*my son does respond to medication but not enough to control or reverse his symptoms. We need to figure out how to increase his medication without fear of side effects".* We asked our interviews and survey respondents what the disadvantages of current treatment and care options were. A majority of parent/caregivers stated that despite the prescribed medications there was little progress or improvement to the patient's physical health. Managing multiple medication regimes and balancing between therapies is very challenging for both patients and parent/caregivers with some relying on the support of multiple specialists on a weekly basis. "*I have seen little progress at the moment it feels like he is stuck…at the moment I am trying to control his reflux, anxiety and depression".* There is an alternative gene therapy targeting a different area of the brain, available outside of the UK, for those living with AADCd. The families in the UK, whom we spoke to during our insight gathering, have travelled to Poland to receive this alternative gene therapy on a compassionate use basis. It is also available on trial, in the USA. **Case Study 1 (Anonymised)** Parent/Caregiver A has a child living with AADCd, patient B. Patient B received an alternative gene therapy 3 years ago in Poland as a young teenager. Prior to the surgery Patient B was on multiple medications to manage symptoms. Parent A states that the medication regime is very complex and the onus was placed on parents/patients to identify the correct dosage through experimenting with amounts and noting the responses. Parent A raised their concern multiple times regarding a lack of support for older children following the surgery and in general. Parent A noted that puberty exacerbated symptoms and created many

	difficulties in managing a growing teenager. Parent A stated that the period following the surgery was 'the most lonely experience' and struggled with the lack of clinical and therapeutic support in the UK. **Case Study 2 (Anonymised)** Parent/Caregiver A has a child living with AADCd, Patient B. Patient B received an alternative gene therapy in Poland 3 years ago as a young child. Since gene therapy, the impact of Patient B's condition has reduced significantly. Patient B has been able to deal with infections far better, has stopped tube feeding all together, has reduced her medication amount significantly, can now vocalise and form words, is able to sit up independently and has begun to learn to walk. Prior to gene therapy, Patient B experienced oculogyric crises most days for hours at a time and since gene therapy their last oculogyric crises happened 10 days following the surgery and has not returned since. In summary, current treatments are symptomatic only. Patients and carers often find these treatments (available in the UK only) for AADCD debilitating, burdensome, complex and onerous, with much uncertainty or hope for the future.
8. Is there an unmet need for patients with this condition?	Yes, there are several unmet needs for patients with this condition. 1. Limited treatment options result in the patient requiring support from multiple specialists, across a range of disciplines and on a frequent basis. Current treatment and care options are both onerous and impact the patient and caregiver quality of life. 2. Medication currently available on the NHS helps patients to manage symptoms but offers little in the way of improvement to overall quality of life. 3. There is a lack of psychosocial support for people living with AADCd and their mental health and social needs often go unmet due to a lack of understanding. 4. There is a lack of understanding amongst general health practitioners resulting in patients being misdiagnosed and/or 'stuck' in incorrect systems and care pathways. 5. Vital early intervention is delayed due to late/incorrect diagnosis.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and parent/caregivers believe eladocagene exuparvovec provides the following advantages. 1. It increases the level of independence and overall freedom of the patient, removing the need for 24-hour care. 2. It relieves suffering. 3. It improves symptoms such as muscle control, ability to eat, improved speech and dyskinesia. 4. It improves overall quality of life. **Case Study 1 (Anonymised)** Parent/Caregiver A has a child living with AADCd, Patient B. Patient B received the eladocagene exuparvovec therapy a year after being diagnosed. Before receiving the therapy Patient B was showing very little improvement and their mobility was severely declining to the extent that Patient B was becoming immobile. Parent/caregiver A describes eladocagene exuparvovec as the "*only option (for Patient B) at the time*" and describes patient B's situation as being "*a matter of life or death".* A month after receiving eladocagene exuparvovec, Patient B began to show marked improvement. Patient B was able to sit up and move themselves independently. Patient B is now able to participate in activities such as swimming and running. Patient B's movements are still limited but are considerably improved. Parent/Caregiver A described the unique challenges he and the family faced after Patient B received the treatment, stating "t*here is a metamorphosis happening from becoming an almost paraplegic child…to a happy child that is running around"*. **Case Study 2** Parent/Caregiver A has a child living with AADCd, Patient B. Patient B received eladocagene exuparvovec in April 2022 but was diagnosed with AADCd in 2019. Before receiving the treatment, Patient B would regularly lose control of eye, limb and neck movement. This resulted in Patient B being unable to cry due to pain. Patient B suffered from a weakening of his chest meaning he could not swallow or digest any liquid and was unable to talk, walk or sit up (failing to reach key milestones for their age). Parent/Caregiver A explained that whilst previous medication reduced the symptoms of Patient B, this treatment provides a step-change in that it solves these symptoms. Parent/Caregiver A explains how significant improvements were seen in just the first few weeks following the surgery, explaining that Patient B can now hold up their neck, open their hands from a fist, has eye control and makes new sounds. Patient B no longer needs to be carried around and is now able to sleep alone given the significantly reduced episodes of dystonia. Parent/Caregiver A notably described how the mood of Patient B has transformed and how the child is no longer "*always angry, always crying*" but is now more interactive and curious, most notably has started to laugh and communicate with his parents.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients and parent/caregivers believe the disadvantages of eladocagene exuparvovec are that it is not a cure for the condition, there may be unwanted complications and side effects and it involves surgery. Patients and carers also expressed a concern regarding the uncertainty of this treatment, questioning its length of efficacy and longer-term side effects. Some patients and carers also expressed concerns regarding aftercare for patients including continual monitoring of residual symptoms and general clinical care. Some parent/caregivers are concerned that the eladocagene exuparvovec only targets the lack of dopamine and not serotonin. Raising concerns, that by only addressing dopamine deficiency, the course of the disease may change and lead to new and novel symptoms as a result of only one neurotransmitter being targeted. One parent/caregiver advised they have sought support from CAMHS to prescribe SSRI's to address these issues and advised that long-term monitoring of patients after receiving gene therapy is vital. Some parents raised concerns regarding gene therapies in general. Stating that gene therapy alone is not enough and must be combined with other therapies for example speech and language and physio in order to gain maximum benefit from the treatment. Additional therapies are required to develop newfound motor functions. Due to the fact that neither of the AADCd gene therapies are available on the NHS, the follow up care, support and safety monitoring has been a concern for many parents in addition to the unknown long-term impact of gene therapy.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is our view that eligibility for this treatment must be considered on a case-by-case basis. Those with a severe phenotype may see increased anatomical and physical benefit versus those with more mild and moderate disease phenotypes. Indications show that there is advantage in early intervention as younger patients are displaying better outcomes. .

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	None
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • The psychosocial and physical impact of living with AADCd is significant, with a majority of parent/caregivers rating their child's quality of life as poor. • Current treatment options available in the UK are symptomatic, often involving multiple medicines, therapies and input from multiple specialists across a number of disciplines. Current treatment options are onerous, burdensome, impact overall quality of life and offer little/no improvement to the patient's physical health and wellbeing. • Parent/caregivers believe eladocagene exuparvovec offers multiple advantages including improved quality of life and relieves some, but not all, of the symptom's patients experience.	

- Some parent/caregivers are concerned regarding the unknown side effects of the therapy, potential unwanted complications, lack of long term data and view the need for surgery as a disadvantage.
- There are multiple unmet needs for people living with this condition, all of which should be taken into consideration during the evaluation process, as the technology has the potential to improve and address some of these needs.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Metabolic Support UK

3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Metabolic Support UK is a non-profit patient umbrella organisation, supporting patients and families worldwide living with Inherited Metabolic Disorders. Metabolic Support UK receives it's funding from corporation, community fundraising and grants, trusts and giving. Metabolic Support UK supports over 20,000 members worldwide.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered from an online AADC Insight survey issued via social media channels and direct mailing. This survey was designed by Metabolic Support UK and the AADC Research Trust. The survey was designed to understand the impact of living with AADC and patients views on current treatment options and Eladocagene exuparvovec. The survey received a total of 8 responses and details of our findings have been included in this submission. Metabolic Support UK and the ADDC Research Trust also hosted a series of recorded insight interviews with patients and caregivers living with AADC. The interviews provided the opportunity to gather further insights regarding the impact of the condition, gather case studies and qualitative views on current and future treatment options. We interviewed 4 number of participants and will shortly publish our findings in a collaborative AADC Insight report.
Living with the condition	
6. What is it like to live with the condition? What do carers	Aromatic L-amino acid decarboxylase deficiency is a genetically inherited neurological disorder which affects the brains' ability to produce neurotransmitters, dopamine and serotonin. Typically, AADCd presents early in life and symptom severity varies based on the individual patient. AADCd is an ultra-rare and debilitating disorder. Patients living with AADCd experience the following symptoms.

experience when caring for someone with the condition?	1. Oculogyric crises 2. Sustained muscle contraction (dystonia) 3. Abnormal posture 4. Involuntary movements (dyskinesia) 5. Tremors 6. Droopy eyelids 7. Temperature instability 8. Low blood pressure (hypotension) 9. Low blood sugar (hypoglycaemia) 10. Seizures 11. Insomnia 12. Gastrointestinal problems 13. Developmental delays 14. Lack of muscle tone (hypotonia) and /or too much muscle tone (hypertonia) 15. Movement disorders 16. Excessive sweating (hyperhidrosis) 17. Nasal congestion, drooling, reflux, and choking 18. Sensitivity to noise and 19. Anxiety, depression, irritability and excessive crying 20. Slow heart rate (bradyarrhythmia) The physical and psychosocial impact of living with AADC is significant. Over 50% of survey respondents rated their child's quality of life as poor. A majority of the respondents had experienced all of the symptoms listed above, with varying degrees of severity between mild and severe. We asked respondents to indicate the symptoms that have the most impact on quality of life

	and the results were as follows; lack of muscle tone (hypotonia), development delays, movement disorders (dyskiesia), excessive sweating (hyperhidrosis), abnormal posture, insomnia, gastrointestinal problems and nasal congestion. The symptoms and manifestations of AADCd also impact a patient's ability to carry out daily activities such as heavy lifting, walking at a fast pace, carrying groceries, completing chores, walking uphill, climbing stairs, bending, lifting, walking short distances, eating, dressing independently and bathing. We asked patients and parent/carers to indicate which of their daily activities have been most impacted as a result of AADCd. The top three activities were walking at a moderate/fast pace, bending or lifting. A large majority (75%) of respondents indicated that their child uses mobility aids and assistive cognitive aids to help them manage daily activities. A majority of respondents have also made physical adaptations to their home to assist their child's daily activities and accessibility. People living with AADCd are not only dependent on assistive equipment and modifications but also the support of external services. 50% of respondents indicated they receive care and support from social services and 37% receive support from a homecare provider. Despite the additional support to manage the condition at home, half of the survey respondents indicated their child had been admitted to hospital within the last 12 months. Over 50% of respondents indicated they do not find the condition easy to manage. The psychological and social impact of AADCd is also significant and AADCd does not just affect the immediate family but also wider family network, including friends and peers. Patients and carers find it difficult to socialise with others, often feel anxious or worried about their future, find it difficult to talk about their feelings, feel isolated and alone, often feel frustrated and unable to cope and seek help from family, friends, professionals for their mental health. **Case study 1 (Anonymised)** Parent/carer X has a child living with AADC, patient Y. Patient Y was initially misdiagnosed with multiple forms of epilepsy. Patient Y's symptoms were short cyclical periods of oculogyric crisis, dystonia and hypertonia. Patient Y was initially prescribed diazepam which worsened their symptoms and L-Dopa which did not improve symptoms. Parent/carer X conducted independent research and following an observation by a specialist and a spinal tap, Patient Y was diagnosed with AADC. **Case study 2 (Anonymised)** Parent/carer A has a child living with AADC, patient B. After noticing developmental delay alongside physical symptoms such as dystonia, the parents of patient B took videos of these episodes and visited over 10 doctors in order to find a diagnosis that went beyond just having seizures. After 2 years, a genetic test confirmed a diagnosis of AADC. The doctor that diagnosed the patient had not previously been aware of AADC. The patient's parents describe the shock when reflecting on the journey to diagnosis as an 'incredible stressful time'. The mother of the patient has had to give up work in

	order to care for the patient and as a family, they avoid leaving their home given it would be so uncomfortable and impractical to do so, resulting in feelings of isolation from society. **Case study 3 (anonymised)** Parent/carer C has a child living with AADC, patient D. Following a multitude of physical symptoms including a failure to thrive and stiffness, an EEG was done to confirm whether symptoms related to seizures. Following different examinations including blood tests and other diagnostic procedures, an AADC diagnosis was confirmed. Following diagnosis Parent C developed symptoms including having no energy, poor sleep, low blood sugar, low weight, which resulted in multiple trips to A&E. As a result of adjusting to the difficult symptoms, continued uncertainty, and feeling of isolation, Parent C experienced a deterioration of their mental health. **Case study 4 (anonymised)** Parent/carer E has a child living with AADC, patient F. After a difficult birth and needing constant comfort alongside what was eventually confirmed to be oculogyric crises lasting up to 8 hours, patient F was assumed by their local hospital and health visitors to have reflux. Following their own research, and a hospitalisation of Patient F elsewhere, AADC was considered, and a lumbar puncture eventually confirmed a diagnosis of AADC. The family have had to stop going out together and have had to adapt life and celebrations around Patient F and their complex regime. Patient F requires multiple and differing medications 4 x daily and as they enter teenage hood, parent E said the management of treatment care is becoming more and more challenging.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most patients manage their condition via prescribed medications such as Vitamin b-6, dopamine receptor agonists (bromocriptine, rotigotine), monoamine oxidase inhibitors and melatonin. A majority of patients rely on a strict dietary regime and sleep schedule to manage their condition. In addition to prescribed medicines, patients also rely on other treatments such as physiotherapy and occupational therapy to manage their condition. 25% of parent/caregivers who took part in our survey, indicated that their child is also in receipt of speech and behavioural therapy to help them manage the condition. One parent/caregiver we interviewed described the current therapy such as physiotherapy and swim therapy as working ‘tremendously’ for their child. Stating that despite the slow progression, their child has demonstrated marked improvement in mobility development and being able to form sentences as a result of speech therapy. We asked our interviewees and survey

	respondents what the other advantages of the current treatment and care options were. Other advantages include improved sleep and reduced severity of dystonia, receiving support from an attentive team, seeing a variety of specialists and a reduction in convulsions. However, despite the advantages, participants indicated there are significantly more drawbacks in relation to current treatment and care options. One respondent stated '*my son does respond to medication but not enough to control or reverse his symptoms. We need to figure out how to increase his medication without fear of side effects'.* We asked our interviews and survey respondents what the disadvantages of current treatment and care options were. A majority of parent/caregivers stated that despite the prescribed medications there was little progress or improvement to the patient's physical health. Managing multiple medication regimes and balancing between therapies is very challenging for both patients and parent/caregivers with some relying on the support of multiple specialists on a weekly basis. "*I have seen little progress at the moment it feels like he is stuck…at the moment I am trying to control his reflux, anxiety and depression".* There are alternative gene therapies available outside of the UK, to those living with AADC. Many of the families in the UK, whom we spoke to during our insight gathering, have travelled to neighbouring countries such as Poland to receive trial gene therapies. **Case Study 1 (Anonymised)** Parent/Caregiver A has a child living with AADC, patient B. Patient B received an alternative gene therapy 3 years ago as a young teenager. Prior to the surgery Patient B was on multiple medications to manage symptoms. Parent A states that the medication regime is very complex, and the onus was placed on parents/patients to identify the correct dosage through experimenting with amounts and noted the responses. Parent A raised their concern multiple times regarding a lack of support for older children following the surgery and in general. Parent A noted that puberty exacerbated symptoms and created many difficulties in managing a growing teenager, Parent A stated that the period following the surgery was 'the most lonely experience' and struggled with the lack of clinical and therapeutic support in the UK. **Case Study 2 (Anonymised)** Parent/Caregiver A has a child living with AADC, patient B. Patient B received an alternative gene therapy in Poland 3 years ago as a young child. Since gene therapy, the impact of Patient B's condition has reduced significantly. Patient B has been able to deal with infections far better, has stopped tube feeding all together, has reduced her medication amount significantly can now vocalise and form words, is able to sit up independently and has begun to learn to walk. Prior to gene therapy, Patient B experienced oculogyric crises most days for hours at a time and since gene therapy their last oculogyric crises happened 10 days following the surgery and has not returned since.

	In summary, patients and carers often find the current treatments (available in the UK only) for AADC debilitating, anxiety inducing and onerous, with much uncertainty or hope for the future.
8. Is there an unmet need for patients with this condition?	Yes, there are several unmet needs for patients with this condition. 1. Limited treatment options result in the patient requiring support from multiple specialists, across a range of disciplines and on a frequent basis. Current treatment and care options are both onerous and impact the patient and caregiver quality of life. 2. Medication currently available on the NHS helps patients to manage symptoms but offers little in the way of improvement to overall quality of life. 3. There is a lack of psychosocial support for people living with AADC and their mental health and social needs often go unmet due to a lack of understanding. 4. There is a lack of understanding amongst general health practitioners resulting in patients being misdiagnosed and/or 'stuck' in incorrect systems and care pathways. 5. Vital early intervention is delayed to late/incorrect diagnosis.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and parent/caregivers believe eladocagene exuparvovec provides the following advantages. 1. It increases the level of independence and overall freedom of the patient, removing the need for 24-hour care. 2. It relieves suffering 3. It improves symptoms such as muscle control, ability to eat, improved speech and dyskinesia 4. It improves overall quality of life. **Case Study 1 (Anonymised)** Parent/Caregiver A has a child living with AADC, patient B. Patient B received the eladocagene exuparvovec therapy a year after being diagnosed. Before receiving the therapy patient B was showing very little improvement and their mobility was severely declining to the extent patient B was becoming immobile. Parent/caregiver A describes eladocagene exuparvovec as

	the 'only option (for patient B) at the time' and describes patient B's situation as being 'a matter of life or death'. A month after receiving eladocagene exuparvovec, patient B began to show marked improvement. Patient B was able to sit up and move themselves independently. Patient B is now able to participate in activities such as swimming and running. Patient B's movements are still limited but are markedly improved. Parent/Caregiver A described the unique challenges he and the family faced after Patient B received the treatment, stating '*there is a metamorphosis happening from becoming an almost paraplegic child…to a happy child that is running around*'. **Case Study 2** Parent/Caregiver A has a child living with AADC, patient B. Patient B received eladocagene exuparvovec in April 2022 but was diagnosed with AADC in 2019. Before receiving the treatment, Patient B would regularly lose control of his eye, limb and neck movement. This resulted in Patient B unable to cry due to pain. Patient B suffered from a weakening of his chest meaning he could not swallow or digest any liquid and was unable to talk, walk or sit up (failing to reach key milestones for their age). Parent/Caregiver B simply describes eladocagene exupavovec as their 'miracle'. They explained that whilst previous medication reduced the symptoms of Patient B, this treatment provides a step-change in that it solves these symptoms. Parent/Caregiver B explains how significant improvements were seen in just the first few weeks following the surgery to administer the treatment, explaining how Patient B can now hold up their neck, open their hands from a fist, has eye control and makes new sounds. Patient B no longer needs carrying around and is now able to sleep alone given significantly reduced episodes of dystonia. Parent/Caregiver B notably described how the mood of Patient B has transformed and how the child is no longer 'always angry, always crying' but is now more interactive and curious, most notably has started to laugh and communicate with his parents.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients and parent/caregivers believe the disadvantages of eladocagene exuparvovec are that it is not a cure for the condition, there may be unwanted complications and side effects and it involves surgery. Patients and carers also expressed a concern regarding the uncertainty of this treatment, questioning its length of efficacy and longer-term side effects. Some patients and carers also expressed concerns regarding aftercare for patients including continual monitoring of residual symptoms and general clinical care. Some parent/caregivers are concerned that the eladocagene exuparvovec only targets the lack of dopamine and not Serotonin. Raising concerns that by only addressing dopamine deficiency, the course of the disease may change and lead to new and novel symptoms as a result of only one neurotransmitter being targeted. One parent/caregiver advised they have sought support from CAMHS to prescribe SSRIs to address these issues and advised the long-term monitoring of their child after receiving gene therapy is vital. Some parents raised concerns regarding gene therapies in general. Stating that gene therapy alone is not enough and must be combined with other therapies such as speech and language, physio etc to gain maximum benefit from the treatment.

	Additional therapies are required to develop motor functions. Due to the fact none of the gene therapies available to AADCd patients are available on the NHS, the follow up care, support and safety monitoring has been a concern and many parents in addition to the unknown long-term impact of gene therapy.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is our view that all current and future patients living with AADC and eligible for this treatment, will benefit from this technology. Younger patients will benefit as the treatment has the potential to improve patient independence and overall quality of life where better outcomes from such early intervention can be realised. Those with a severe phenotype may see increased anatomical and physical benefit versus those with more mild and moderate disease phenotypes (but such benefit would still be realised)
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The psychosocial and physical impact of living with AADC is significant, with a majority of parent/caregivers rating their child's quality of life as poor.
- Current treatment options available in the UK often involve multiple medicines, therapies and input from multiple specialists across a number of disciplines. Current treatment options are onerous, impact overall quality of life and offer little/no improvement to the patient's physical health and wellbeing.
- Parent/caregivers believe eladocagene exuparvovec offers multiple advantages including improved quality of life and relieves some of the symptom's patients experience.
- Some parent/caregivers are concerned regarding the unknown side effects of the therapy, potential unwanted complications and view the need for surgery as a disadvantage.
- There are multiple unmet needs for people living with this condition, all of which should be taken into consideration during the evaluation process, as the technology has the potential to improve and address some of these needs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Case Study 1

Parent/Carer: X
Patient: Y
Condition: Aromatic Amino Acid Decarboxylase deficiency

Diagnosis Journey

At the age of 3 months, Parent X's daughter started showing symptoms of being "*floppy*", not reaching milestones and tensing up "*whilst her eyes crossed, and her limbs twisted*". After a GP suspected these episodes to be epilepsy, Parent X's daughter was put on Diazepam and was given an EEG; the results of which came back normal. After realising there were no triggers to these episodes, and therefore dismissing multiple epilepsy diagnoses, she was diagnosed with having a dystonia disorder and put on L-Dopa which didn't alleviate her symptoms. Parent X and his partner sought other professional opinions in Thailand and Singapore and researched her symptoms themselves in which AADCd became a possibility. An eventual observation and lumbar puncture confirmed their daughter had AADCd.

Key Symptoms and Impact

Prior to Parent X's daughters' diagnosis, she experienced what was later confirmed as oculogyric crises, dystonia and hypertonia. She also experienced difficulty eating, communicating and movement. The family's lifestyle has changed significantly and came to a "*screeching stop*", from travelling the world to creating the "*SOS: Sit On Sofa*" group, not wanting to go outside and trigger what they thought were seizures. Leisure activities have had to change but they've got to a point where the family have found a healthy balance being able to adapt activities so that they're 'accomplishing [their] goals as parents, and wanting to push her, but also making memories. "*Life is totally different, but a good different*".

Current Treatment and Care

Prior to gene therapy, Parent X's daughter received Selegiline, Rotigotine patches, and Benzaprine, although the latter only helped to space out her episodes. Her current medication includes Vitamin B6 and PS128, but they focus on diet, a strict sleep schedule and other forms of therapy. Physical therapy, sleep therapy, horse therapy and speech therapy have been beneficial in allowing her to move and manipulate herself more as her body gets stronger.

Experience with Eladocagene Exuparvovec

Although initially concerned as to whether gene therapy would be beneficial for her phenotype, both parents considered the procedure as a "*life or death*" opportunity, that it was the "*only option at the time*". Since gene therapy, "*every day has been a miracle*". She experienced dyskinesia initially following the surgery, but her abilities have begun to develop ever since. She is now able to sit up, run, swim underwater, pull herself up and out of the pool, is currently learning how to jump and was able to recover quickly from a broken bone. Parent X explains how there is a "*metamorphosis*" following gene therapy in which his "*paraplegic almost*" child became a "*happy girl that's running around*".

> “There's this transition that's happening, it's a metamorphosis, where they're going from totally unable to move to this happy girl that's running around and giggling and laughing ”

Case Study 2

Parent/Carer: A
Patient: B
Condition: Aromatic Amino Acid Decarboxylase deficiency

Diagnosis Journey

Following Parent A's sons' birth, Parent A and his partner noticed developmental delay alongside physical symptoms including abnormal movements (dystonia). They took videos of these episodes and visited over 10 doctors in multiple different countries, and it was thought to be seizures. His parents refused any treatments for seizures at this time because, as they explain it, they knew this diagnosis wasn't "*true*". After an EEG and an MRI showed no unusual activity in his brain and after 2 years of seeking a diagnosis a genetic test confirmed Parent A's son had AADC. The doctor that diagnosed him had not previously been aware of AADCd himself and had to conduct research in order to understand the condition. Parent A and his partner were in "*shock" at the diagnosis*, saying it '*changed their lives'* and explain the journey was a "*very stressful time*".

Key Symptoms and Impact

Parent A's son experiences gastrointenstinal issues, hypertonia and dystonia. His dystonia is the most troublesome symptom; during episodes, he is unable to do anything and loses control of his eye, limb and neck movement. He tries to cry but cannot, his muscles become painful, and it has weakened his chest. His parents explain that they are "*waiting for dystonia"*, waiting for the next inevitable episode. The weakening of his chest has meant he can no longer swallow and digest any liquid, confirmed by a swallowing video test, and so has had a tube fitted in his stomach for all liquid and medication. His symptoms have also meant he is unable to talk, walk or sit up. The impact of his symptoms has meant that they find it difficult to go out as a family and, prior to his gene therapy, they preferred to stay home or go out individually to reduce his discomfort.

Current Treatment and Care

Parent A's sons' medication has not changed since his correct diagnosis; he is on bromocriptine, vitamin B6 and selegiline and takes these multiple times a day. His medication has improved and reduced his symptoms. He currently has no specific diet plan, and his food is varied, although

mushed up to make it easier to swallow and digest, and all liquid and medication is taken through a stomach tube. Rather than eating three full meals, he eats every 2 hours in an effort to encourage weight gain, this has not yet been successful, and he has been the same weight for most of his infancy. He has previously tried physical therapy but due to his distress during multiple attempts with different physical therapists, this has not been consistent. Due to the constant care that he needs, his mother has given up work and explains that it would be difficult to find work as a result of the additional flexibility she needs in order to look after him.

Experiences with Eladocagene Exuparvovec

Despite, at the time, living in the United Arab Emirates, after finding out about gene therapy clinical trials occurring in the United States via the internet, his parents applied to multiple hospitals and quickly heard back from Texas Children's Hospital. Following their approval, within 2 months they moved to the USA. When asked about the disadvantages, they had none to give but mentioned that recovery meant staying in the hospital the week following, and the dyskinesia his body experienced as it started to move meant his mouth muscles weren't working properly and he couldn't eat for 2 weeks. Improvements were seen after 1-2 weeks following the surgery. He is now able to hold up his neck, can open his hands from a fist, has eye control and makes new sounds; this has allowed him to begin 'discovering' his surroundings and touching his face. For his parents, it has meant they are able to play with him more, and no longer need to carry him around but can leave him alone as he understands they'll come back shortly and therefore does not cry as frequently as before. Similarly, his parents describe how his general "*mood has changed*". Beforehand he was "*always angry, always crying*" but has since been more interactive and is no longer afraid of other children but laughs with and tries to communicate with them. His dystonia now only lasts up to an hour, and he is able to sleep alone and much better as a result. His mother explained that although previous medication reduced his symptoms, gene therapy is "*solving"* them, and it's been a "*miracle*". Both parents agreed that gene therapy has made "*life easier*" for themselves and their son and that it has been "*the best choice for him*".

> “Before the gene therapy, he was afraid of children, he was afraid of people, he didn't like the lights and we could not enter the mall but afterwards he likes playing with the kids, laughing, trying to speak with them ”

Case Study 3

Parent/Carer: C
Patient: D
Condition: Aromatic Amino Acid Decarboxylase deficiency

Diagnosis Journey

Parent C's daughter experienced consistently poor feeding, defined as a "*failure to thrive*" by medical professionals, alongside a multitude of other concerning symptoms including episodes of stiffness and eye fixation. During a paediatrician appointment, Parent C applied pressure to the doctors requesting additional tests which resulted in having an EEG to determine whether the episodes that she was experiencing were seizures or dystonia. This was followed by multiple different examinations including blood tests and a lumbar puncture. After a very "*traumatic*" and difficult few months, Parent C felt a sense of "*relief*" following the diagnosis despite there being continued uncertainty.

Key Symptoms & Impact

Prior to gene therapy, Parent C's daughter was always unsettled, crying throughout the day and night, would projectile vomit several times daily, was poor at feeding, experienced oculogyric crises most days for hours at a time, had episodes of apnoea and episodes of stiffness and fixated eyes. These symptoms meant she had no energy, poor sleep, low blood sugar, low weight and experienced many trips to A&E. The impact of these symptoms resulted in a decline of Parent C's mental health; she felt she had been "*thrown in the deep end*", found it stressful and difficult to maintain her high-pressured job, had become completely "*isolated*" and, feeling close to breaking point, had even considered whether giving her daughter up for adoption was an option, as she struggled to support two children, one with a very rare and complex disorder.

Current Treatment and Care

Parent C's daughter **received an alternative AAV2-AADC gene therapy in Poland**. Prior to gene therapy, Parent C's daughter had to consistently use a feeding tube 20 hours a day and was on approximately 15 different medications. Moreover, as a result of constant difficult symptoms, she would be put on antibiotics which meant she was unable to tolerate food very well. She is currently on calcium folinate, a nasal spray and melatonin. Since gene therapy, she has been able to produce her own dopamine which has allowed her to be taken off other previous medications for this purpose. She has also started learning to walk with an assistive walker and uses a saline nebuliser at night. She also accesses physiotherapy and speech therapy.

Previously, the family had a personal assistant 4 hours a week to provide her parents with some respite and time to spend with her older sibling. Her mother explains that following gene therapy "*there wasn't anything that could be offered to improve her treatment plan".*

Gene therapy has allowed Parent C's daughter to make "*remarkable progress*", since gene therapy the impact of her condition has reduced significantly. She is able to deal with infections far better, has stopped tube feeding all together, has reduced her medication significantly, can now vocalise and form words, is able to sit up independently and has begun to learn how to walk, her independence has improved, her eating has improved, and her last oculogyric crises episode happened 10 days following gene therapy and has not returned since. Although her mother acknowledges the "*complete risk"* of being a "*guinea pig"* for the trial, she feels there were no disadvantages.

> “ She was just not settled at all, she didn't sleep all night, she'd cry all night, she'd cry all day; obviously she was in so much pain and I didn't really know what was going on at the time ”

Case Study 4

Parent/Carer: E
Patient: F
Condition: Aromatic Amino Acid Decarboxylase deficiency (AADCd)

Diagnosis Journey

After a difficult birth, Parent E's son would not latch onto his mother and would only take to a certain kind of bottle and teat and was very thin as a result. At 3 months, he would cry most of the time without constant comfort, had trouble maintaining a sleep schedule and kept experiencing what was eventually confirmed to be oculogyric crises lasting up to 8 hours. During this time, his local hospital and health visitor kept assuming that these symptoms were as a result of reflux; it was only following Parent E's own research of the symptoms being experienced that she considered AADCd as a possibility. During hospitalisation whilst on holiday elsewhere in the UK, it was explained that it was likely a genetic condition and encouraged them to test. After several brain scans, EEGs and heart tests came back normal, a lumbar puncture gave the confirmed diagnosis of AADCd.

Key Symptoms and Impact

Parent E described her sons' symptoms as "*severe*"; with oculogyric crises every 3 days up, no head, torso or limb control, fatigue, mood swings, sensitivity to light and noise, vomiting and constipation. The oculogyric crises were especially difficult to deal with; Parent E stated her son's days would be "*wasted*" as a result, with celebrations and days out cut short and spoilt. Although the parents have been given times of respite as a result of family support and a continuing care package from the NHS, the impact on the family has meant they've stopped going out together and have had to adapt life around him and his "*very complex regime*".

Current Treatment and Care

Following diagnosis, Parent E's son was put on a "*concoction*" of different medicines and Parent E and her partner felt they were left to figure out what balance of these were correct for their son. These medications included pyridoxal phosphate which was "*horrendous to try to swallow*" and dopamine replacement medication, that could set off dyskinesia if the dose was too high. These were given 4 times a day, at specific times; to not stick to the specific time intervals would cause dyskinesia which would result in moodiness and crying. At 7 years, a G peg was fitted so that his medication could be administered this way. This previous medication plan did improve

symptoms such as attempting to move even if the action was not complete, and it was able to stabilise his mood. His medication currently includes no neurological tablets, omeprazole, folic acid, bromide and fluoxetine.

Parent E's son **received an alternative AAV2-AADC gene therapy in Poland.** Following gene therapy, Parent E had wished for further support given, especially as her son approaches puberty. Parent E feels her son would benefit from further therapies and they have since sought treatment from a private physiotherapist.

Parent E and her partner underwent a fundraising process to enable their son access to the experimental gene therapy, not supported by the NHS. The fundraising process was stressful and "*exhausting*" for the family and Parent E describes it as "*the worst process*" she has to do in her life, with the added pressure of ensuring her child was able to get the opportunity for a better life; there was no support from the NHS.

Initially, following the surgery, Parent E's son was "*vacant*" then experienced "*horrendous dyskinesia*" and was unable to eat anything; "*it was almost like his body had shut down and was starting again"*. During this "*very, very lonely*" time, his mother reiterates the lack of support and understanding from doctors, despite his age and puberty exacerbating symptoms and making it difficult to manage him.

Since receiving gene therapy Parent E's son initially started to control his neck and torso, sit up after a few months, move his arm and make a grabbing motion, has begun to attempt to walk and vocalise. After 6 months he was able to eat full meals and snacks and experienced "*the joy of food"*. Parent E explains "*he's thriving now*" and is "*developing so much more than [she] ever though he would"*, but, again, mentions that support is needed for older children following gene therapy. Other than the difficult initial symptoms, a disadvantage given was that the gene therapy didn't target the serotonin part of his brain.

> “He's developing so much more than I ever thought he would but for older children ... they need that support mentally”

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **x**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for aromatic L-amino acid decarboxylase deficiency

7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is not a nationally commissioned highly specialised service (HSS) for the treatment of aromatic L-amino acid decarboxylase deficiency. Given the small number of patients expertise is limited to a small number of quaternary centres.
8. What impact would the technology have on the current pathway of care?	Patients may need to access gene therapy at a provider that was not their usual centre of care
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This therapy is not commissioned for routine use by NHS England.
10. Will the technology be used (or is it already used) in	The therapy would be administered through a centre that had the appropriate infrastructure to support the safe administration and surveillance of this specific gene therapy.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option for this patient cohort.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The therapy would be administered through a centre that had the appropriate infrastructure to support the safe administration and surveillance of this specific gene therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There may be an additional local tariff paid by NHSE for administration
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	

11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency

ERRATUM

Post factual accuracy check version with corrections

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Neelam Kalita, Senior Research Fellow, Health Economics Inês Souto Ribeiro, Senior Research Assistant, Health Economics Karen Pickett, Senior Research Fellow, Evidence Synthesis Emma Maund, Research Fellow, Evidence Synthesis Lois Woods, Senior Research Assistant, Evidence Synthesis David Alexander Scott, Principal Research Fellow, Statistics Asyl Hawa, Research Fellow, Health Economics Joanne Lord, Professorial Research Fellow, Health Economics
Correspondence to	Dr Karen Pickett Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
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Declared competing interests of the authors and advisors

The authors report none. Prof Manju Kurian reports no financial relationships or interests with the company in the previous 12 months. Prof Kurian reports the following non-financial interests associated with the technology under appraisal: She has been involved in discussions with PTC Therapeutics about Great Ormond Street Hospital bidding to be one of the clinical sites for eladocagene exuparvovec gene therapy. Prof Kurian has also undertaken research work on an alternative gene therapy approach using a similar viral vector; her research group was not financially renumerated for this work. Additionally, Prof Kurian is on the medical and scientific advisory board for the AADC Research Trust. The Trust have nominated her as a clinical expert for this appraisal for the National Institute for Health and Care Excellence (NICE).

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Inês Souto Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review, indirect treatment comparison feasibility assessment, and the Natural History Database (NHDB), drafted the report, project managed the review, and is the project guarantor; Emma Maund critically appraised the clinical effectiveness systematic review and the NHDB, and drafted the report; Lois Woods critically appraised the company's systematic literature review searches, critically appraised the clinical effectiveness systematic review, searched for ongoing studies and drafted the report; David Alexander Scott critically appraised the indirect treatment comparison feasibility assessment and the NHDB, and drafted the report; Asyl Hawa critically appraised the economic evaluation, and drafted the report; Joanne Lord critically appraised the economic evaluation, and drafted the report.

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LIST OF ABBREVIATIONS

AADC	Aromatic L-amino acid decarboxylase
AE	Adverse event
AIC	Academic in confidence
BNF	British National Formulary
CASP	Critical appraisal skills programme
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
EMBASE	Excerpta Medica database
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
GMFM-88	Gross motor function measure
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
iNTD	International Working Group on Neurotransmitter Related Disorders
IPD	Individual patient level data
ITC	Indirect treatment comparison
ITT	Intent to treat
LOCF	Last observation carried forward
LS	Least squares
MEDLINE	Medical Literature Analysis and Retrieval System Online
mITT	Modified intent to treat

NHDB	Natural history database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PAS	Patient Access Scheme
PDMS-2	Peabody Developmental Motor Scales Second Edition
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0 to **Error! Reference source not found.** explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (see section 2).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID3850	Summary of issue	Report sections
1	Uncertainty whether all relevant data have been included in the CS	3.2.1.6 and 3.7
2	Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	3.2.1.5, 3.2.5.1 and 3.7
3	It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived	3.2.6 and 4.2.6.1.1
4	Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	3.2.6 and 3.7
5	Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	4.2.5 and 6.2
6	Use of PDMS-2 scores to predict motor milestone achievement	4.2.6.1.1 and 6.2
7	Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	4.2.6.3, 6.1 and 6.2
8	The survival extrapolation methods used by the company overestimate survival	4.2.6.2 and 6.2
9	It is unclear how reflective the company's resource use estimates are of clinical practice	4.2.8 and 6.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company applies a discount rate of 1.5% for both costs and effects, whereas the EAG are unclear whether this appropriate.
- The company uses a Bayesian growth curve model using PDMS-2 scores to predict motor milestone development, whereas the EAG prefers to use the observed patient distribution across the motor milestone health states from the three eladocagene exuparvovec clinical studies.
- The company uses the log-logistic parametric curve to extrapolate survival in the motor milestone states – 'no motor function', 'full head control', 'sitting with assistance' and 'standing with support' – whereas the EAG prefers to use the Weibull parametric curve for these states.
- The EAG prefers to use the resource use estimates based on our clinical expert advice.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new health technology extends length of life and improves health-related quality of life in comparison to existing health technologies. This is expressed in terms of incremental quality-adjusted life years (QALYs) gained. An ICER is the ratio of the additional cost of the new technology for every QALY gained.

Table 2 and Table 3 report the company's cost effectiveness base case results using the list price and patient access scheme (PAS) price of eladocagene exuparvovec, respectively. These results, which were updated in response to EAG clarification questions B2, B12 to 14 and B19 to 21, show that eladocagene exuparvovec is [redacted] and yields [redacted] than best supportive care, resulting in an ICER of £176,617 per QALY (using the list price of eladocagene exuparvovec) and [redacted] per QALY (using the PAS price). The company applied a QALY modifier factor of [redacted] as their undiscounted incremental QALY gain per patient from eladocagene exuparvovec versus best supportive care over a lifetime horizon was between 10 and 30.

The model results were most sensitive to the use of a QALY modifier, alternative discount rates, utility values, and modelling the motor milestones achievement directly from the observed distributions in the eladocagene exuparvovec trials. Other assumptions such as using asymptotic distribution for the Bayesian growth curve model, survival extrapolation

based on a proxy condition, spinal muscular atrophy, and caregiver disutilities also had a significant impact on the cost effectiveness results.

Table 2 Company's revised base case results (discounted at 1.5%, list price for eladocagene exuparvovec, QALY modifier applied)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,617	-13.75

Source: reproduced from Table 29 of the company's response to clarification questions.
[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 3 Company's revised base case results (discounted at 1.5%, PAS price for eladocagene exuparvovec, QALY modifier applied)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: reproduced from Table 30 of the company's response to clarification questions.
[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

1.3 The decision problem: summary of the EAG's key issues

The EAG has not identified any key issues related to the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Uncertainty whether all relevant data have been included in the CS

Report section	3.2.1.6 and 3.7
Description of issue and why the EAG has identified it as important	The EAG identified three studies of AAV-hAADC-2 administered into the putamen, conducted in Japan. It was unclear to the EAG if the vector used in these studies was the same as the one used in the eladocagene exuparvovec studies; the studies' publication describes the vector as similar to that used in the eladocagene exuparvovec studies. We assume this means it is not the same, but

	believe it would be useful to obtain confirmation that this evidence is not relevant to the appraisal.
What alternative approach has the EAG suggested?	If the studies conducted in Japan, identified by the EAG, used the same vector as in the eladocagene exuparvovec studies, the results should be summarised for consideration in this appraisal.
What is the expected effect on the cost-effectiveness estimates?	Unknown. If not all relevant eladocagene exuparvovec effectiveness evidence has been included in the CS, this may affect the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	We suggest the company clarify if the vector used in the studies conducted in Japan was the same as the one used in the eladocagene exuparvovec studies. Clinical expert opinion about this would also be useful for resolving this uncertainty. The EAG also suggests that clinical experts and other stakeholders are asked during technical engagement if they are aware of any relevant studies that have not been included in the CS.

Issue 2 Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery

Report section	3.2.1.5, 3.2.5.1 and 3.7
Description of issue and why the EAG has identified it as important	A strength of the eladocagene exuparvovec trials included in the CS was the long-term follow-up of [redacted] of the enrolled 30 participants beyond five years post-surgery (in two of the three studies; AADC-010 and AADC-CU/1601). However, the length of time the participants were followed-up varied, with small numbers of participants with data available at the longest follow-up timepoints (84 and 120 months, respectively), making the results uncertain. It is also unclear how participants were selected to continue in the studies and reasons for attrition. It is therefore uncertain if those who were followed up differed to those who were not in a way that may potentially bias the results. Thus, the longer-term efficacy of eladocagene exuparvovec beyond five years is uncertain.
What alternative approach has the EAG suggested?	We recognise that this is the nature of the data collected, but it would be useful to understand how participants progressed into the follow-up part of the studies and reasons for attrition. This would clarify whether there is a risk of bias associated with the longer-term results.
What is the expected effect on the cost-effectiveness estimates?	The long-term data between beyond five years and up to 10 years post-surgery aids the validation of the assumptions used in the company's- and the EAG's economic models base case and scenario analyses. More information to determine risk of bias would be informative for this validation.
What additional evidence or analyses	Information from the company about what determined whether participants entered into the follow-up phase of

might help to resolve this key issue?	the studies and reasons for attrition from the studies between and including five years post-surgery and the longest follow-up timepoint in each study.

Issue 3 It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived

Report section	3.2.6 and **Error! Reference source not found.**
Description of issue and why the EAG has identified it as important	The EAG cannot check the accuracy of the pooled proportions of participants from each trial achieving the motor milestones used in a company economic model scenario analysis and in the EAG's base case. This is because: • The EAG does not have access to individual participant data to be able to check the figures. • The data provided in the model is for the highest motor milestone achieved, while the aggregate results presented in the clinical effectiveness section of the CS is not presented in this way. • For the LOCF approach, the numerator and denominators are not provided in CS or in the economic model. It is also uncertain how these data were derived as: o It is unclear why data from only 28 of the 30 enrolled participants are used in the pooled analysis. o It is unclear if the long-term follow-up data collected between 12 and 60 months in study AADC-011 have been used in the company's model.
What alternative approach has the EAG suggested?	We suggest that data from all 30 participants are included in the pooled analysis as well as the long-term data from the AADC-011 study, if this has not already been used.
What is the expected effect on the cost-effectiveness estimates?	The effect is unknown. However, as the three eladocagene exuparvovec studies had a collectively small sample size (N = 30), the model results are quite sensitive to the motor milestone achievement distribution.
What additional evidence or analyses might help to resolve this key issue?	Clarification from the company about how the patient distributions were derived would be appreciated. We suggest that they provide (i) the underlying calculations and rationale to derive the pooled estimates for all of the three motor milestone achievement distributions available in the economic model; (ii) the reasons for excluding two participants (and a scenario analysis including them); (iii) clarification of whether the long-term data from the AADC-011 study (collected between after 12 and up to 60 months post-surgery) was incorporated into the economic model (and, if not, a scenario analysis including it).

Issue 4 Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies

Report section	3.2.6 and 3.7
Description of issue and why the EAG has identified it as important	The company used the LOCF approach to impute missing data in a pooled analysis of the motor milestone achievement results from the eladocagene exuparvovec studies (that is, the results pooled between baseline and up to five years post-surgery). These data were used in a company scenario analysis and the EAG's base case. We generally considered this approach acceptable in the context of AADC deficiency treatment with eladocagene exuparvovec. We note two uncertainties, however, about using the LOCF method: • It is unclear how much missing data were imputed. • The approach relies on the assumption that people with AADC deficiency maintain their motor milestone achievement over time (i.e. up to five years post-surgery) and do not experience a decline. A decline is theoretically possible, plus two participants in the eladocagene exuparvovec studies experienced a decline in their motor scores three- and five-years post-surgery, respectively.[1] It is unclear if any other participants (with data) showed a decline over time. This issue has a significant impact on the cost-effectiveness estimates.
What alternative approach has the EAG suggested?	The EAG used the LOCF approach for our preferred base case, but tested this assumption in a set of scenario analyses using, a) a dataset in the model that calculates the proportions achieving the motor milestones using the baseline number of participants as the denominator (no missing data were imputed), and b) a dataset with the proportions calculated using the number of participants followed-up at each timepoint as the denominator.
What is the expected effect on the cost-effectiveness estimates?	The EAG base case ICER (using the LOCF approach) is [redacted] (discounted at 0%), [redacted] (1.5%) and [redacted] (3.5%) per QALY for eladocagene exuparvovec versus best supportive care (using the PAS price). The EAG scenario analyses show that using the observed data based on the baseline denominator results in an ICER of [redacted](0%), [redacted](1.5%) and [redacted] (3.5%) per QALY. The scenario using the follow-up denominator results in ICERs of [redacted](0%), [redacted] (1.5%) and [redacted] (3.5%) per QALY.
What additional evidence or analyses might help to resolve this key issue?	The following information will aid us in fully determining the appropriateness of the LOCF approach: • the extent of missing data and the extent imputed.

	• whether any other participants (with data) experienced a decline at any point between baseline and five years

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%

Report section	4.2.5 and **Error! Reference source not found.**
Description of issue and why the EAG has identified it as important	The NICE manual suggests that a discount rate of 1.5% may be considered if: i) the technology is for people who would otherwise die or have a very severely impaired life; ii) it is likely to restore them to full or near-full health; and iii) the benefits are sustained over a very long period. While we view that eladocagene exuparvovec is targeted for patients with severely impaired life, it remains unclear if the technology will restore patients to full or near-full health and whether the benefits will persist in the long-term. Advice from our clinical expert suggests that eladocagene exuparvovec is unlikely to restore patients with AADC deficiency to full or near-full health. Secondly, there is currently no data to support persistence of treatment benefit in the long-term beyond 10 years.
What alternative approach has the EAG suggested?	The EAG considers that a discount rate of 3.5% is appropriate for costs and effects. However, considering the uncertainties, we opted to present the cost-effectiveness results of the EAG analyses using 0%, 1.5% and 3.5% discount rates to illustrate the impact of this assumption on the overall cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	The results of the EAG's preferred base case (using PAS price) with varying discount rates are as follows: • 0% for both costs and effects: [redacted] per QALY • 1.5% for both costs and effects: [redacted] per QALY • 3.5% for both costs and effects: [redacted] per QALY
What additional evidence or analyses might help to resolve this key issue?	Further information and expert opinion on treatment benefit and plausibility of its persistence in the long-term.

Issue 6 Use of PDMS-2 scores to predict motor milestone achievement

Report section	**Error! Reference source not found.** and **Error! Reference source not found.**
Description of issue and why the EAG has identified it as important	The company uses a Bayesian growth curve model using PDMS-2 scores to predict motor milestone development. We have concerns about using PDMS-2 scores to predict motor milestones because: • Assessment of motor milestones in NHS practice is usually not based on formal motor scales. The motor milestone achievement states are more

	reflective of how motor function is assessed in practice than the PDMS-2 scores. • Comparing the company's predicted distribution of patients with the observed distribution from the trials, we note that the predicted estimates (using PDMS-2 scores) in the 'worst' health state - 'no motor function' - are lower than the observed values. Whereas for the 'best' motor milestone state - 'walking with assistance' - the predicted estimates are significantly higher than the observed distribution. This indicates that using the predicted motor milestone health states would potentially overestimate the effectiveness of eladocagene exuparvovec, favouring the eladocagene exuparvovec compared to best supportive care. • Using the observed patient distribution for eladocagene exuparvovec is consistent with the approach adopted for best supportive care.
What alternative approach has the EAG suggested?	We prefer to use the observed motor milestone achievement results from the eladocagene exuparvovec trials, rather than predicting them using the PDMS-2 score, in our base case.
What is the expected effect on the cost-effectiveness estimates?	The EAG base case ICER (which uses the observed distribution across the motor milestone health states) is [redacted] (discounted at 0%), [redacted] (1.5%) and [redacted] (3.5%) per QALY for eladocagene exuparvovec versus best supportive care (using the PAS price). Using the company's approach (using PDMS-2 scores as a predictor of motor milestone achievement) reduces the ICERs to [redacted](0%), [redacted](1.5%) and [redacted] (3.5%) per QALY.
What additional evidence or analyses might help to resolve this key issue?	Additional expert clinical opinion about the appropriateness of using the PDMS-2 score to predict motor milestone achievement results may provide more clarity on this issue.

Issue 7 Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes

Report section	**Error! Reference source not found.**, 6.1 and 6.2
Description of issue and why the EAG has identified it as important	The company assumes that the treatment effect of eladocagene exuparvovec persists over patients' lifetime. We note that this assumption is uncertain due to a lack of longer follow up data beyond 10 years post-surgery.
What alternative approach has the EAG suggested?	The EAG conducted a set of conservative exploratory scenario analyses to test the impact of treatment waning on the cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	The results of the EAG scenarios show that treatment waning has a significant impact in the cost-effectiveness estimates, with results varying between ICERs of [redacted](0%), [redacted](1.5%) and [redacted] (3.5%) per

	QALY, if a gradual decline from year 25 onwards is assumed, and ICERs of [redacted](0%), [redacted](1.5%) and [redacted] (3.5%) per QALY, if a sudden decline at year 25 is assumed, after which people's motor milestone achievement is the same as for best supportive care.
What additional evidence or analyses might help to resolve this key issue?	Further discussion and clinical expert opinion about whether the treatment effect of eladocagene exuparvovec will persist over a patient's lifetime or plausibly wane.

Issue 8 The survival extrapolation methods used by the company overestimate survival

Report section	4.2.6.2 and 6.2
Description of issue and why the EAG has identified it as important	For long term survival, both log-logistic and Weibull provide a good fit to the observed data until 30 years. Beyond 30 years, the Weibull provides lower survival estimates compared to log-logistic for all health states. However, extrapolating survival using Weibull (and log-logistic) predicts similar survival for patients in "standing with support" and "walking with assistance" beyond 45 years. We are unclear whether this is plausible. We also note that using exponential overestimates the survival of patients in the "walking with assistance" health state, which potentially benefits eladocagene exuparvovec.
What alternative approach has the EAG suggested?	The EAG uses an exponential distribution for 'walking with assistance' and a Weibull distribution for the remaining health states in our base case. We also conducted a scenario analysis using the Weibull distribution for all health states.
What is the expected effect on the cost-effectiveness estimates?	The EAG base case (assuming exponential for "walking with assistance" and Weibull for the other health states) yields an ICER of [redacted] (discounted at 0%), [redacted] (1.5%) and [redacted] (3.5%) per QALY (using the PAS price). Using the company's base case assumption (exponential for "walking with assistance" and log-logistic for the other health states) changes the ICER to [redacted](0%), [redacted](1.5%) [redacted] (3.5%) per QALY, while assuming Weibull to extrapolate survival in all health states increases the ICER to [redacted](0%), [redacted](1.5%) and [redacted] (3.5%) per QALY.
What additional evidence or analyses might help to resolve this key issue?	Additional expert clinical opinion about the plausibility of similar survival in the "standing with support" and "walking with assistance" health states may provide more clarity on this issue.

Issue 9 It is unclear how reflective the company's resource use estimates are of clinical practice

Report section	4.2.8 and 6.2

Description of issue and why the EAG has identified it as important	The clinical expert advising the EAG agreed with most of the resource use estimates used in the company's model but identified some discrepancies between the company's estimates and her experience in clinical practice in the NHS.
What alternative approach has the EAG suggested?	The EAG used the estimates suggested by our clinical expert in the EAG's preferred base case.
What is the expected effect on the cost-effectiveness estimates?	The EAG base case (using our clinical expert's estimates) yields an ICER of [redacted] (discounted at 0%), [redacted] (1.5%) and [redacted] (3.5%) per QALY (using PAS price) compared to [redacted](0%), [redacted](1.5%) and [redacted] (3.5%) per QALY when using the company's base case assumptions.
What additional evidence or analyses might help to resolve this key issue?	Additional expert clinical opinion about the resource use associated with treating AADC deficiency and the introduction of eladocagene exuparvovec into clinical practice may be informative to assess consensus.

1.6 Other key issues: summary of the EAG's view

The EAG have not identified any other key issues that we believe will materially affect decision making.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAG preferred model assumptions are as follows:

1. **Baseline age and weight of population**: 6 years and 15 kg
2. **Discount rate of costs and effects**: We consider that a discount rate of 3.5% is appropriate (more details in section 4.2.5) as opposed to the company's base case which presents the results discounted at 1.5%. However, due to the high uncertainty around this assumption, we present the EAG results for the discount rates of 0%, 1.5% and 3.5%.
3. **Motor milestone achievement (eladocagene exuparvovec)**: Use the trial observed distribution of patients across the motor milestone health states using the LOCF approach to impute missing data.
4. **Adverse events**: Occurring in ≥5% of patients in the trial.
5. **Extrapolation of survival curves**: Weibull parametric curve to extrapolate survival in all health states of the model, except for the "walking with assistance" (exponential).
6. **Update costs to the most recent price**: All costs are updated to 2021/2022 prices by using the British National Formulary (BNF) 2022 prices [2] or inflating based on the PSSRU inflation indices for 2020/2021.[3]

7. **Resource use estimates**: based on estimates informed by the EAG's clinical expert.
8. **Number of carers**: based on our expert's advice, we assume patients in the most severe health state (no motor function) require 2.5 carers while patients in the other health states require two carers.

The results of the EAG corrected company base case are presented in Table 48. Table 4 reports the EAG preferred base case results for eladocagene exuparvovec vs best supportive care which shows that the ICER of eladocagene exuparvovec versus best supportive care changes from [redacted] per QALY (discounted at 1.5%) in the company's revised base case (EAG corrected) to [redacted] per QALY (discounted at 3.5%) or [redacted] (discounted at 1.5%) using the PAS price.

Table 4 Cumulative change from the EAG corrected company base case to the EAG preferred base case (discounted at 0%, 1.5% and 3.5%, using PAS price of eladocagene exuparvovec, QALY modifier applied)

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER (£/QALY)		
		3.5%	3.5%	0%	1.5%	3.5%
EAG corrected company base case	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Age and weight: 6 years and 15kg	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Motor milestone achievement: observed data	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Adverse events: ≥5%	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Extrapolation of survival: Weibull + exponential	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Updated costs	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Resource use estimates: EAG expert	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Number of carers: 2.5 for no motor function and 2 for the other health states	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred base case	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC, best supportive care; EAG, External Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to the National Institute for Health and Care Excellence (NICE) from PTC Therapeutics on the clinical effectiveness and cost effectiveness of eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase (AADC) deficiency. It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 10th June 2022. A response from the company via NICE was received by the EAG on 27th June 2022 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on aromatic L-amino acid decarboxylase deficiency

The EAG considers that the company provides a clear and accurate description of AADC deficiency (CS section B.1.3), with the exception of describing people with the severe phenotype as "bedridden" (CS section B.1.3.3.2; see our comment on this in section 2.2.1.3).

AADC deficiency is a rare, autosomal recessive neurometabolic condition.[4,5] As described in the CS, AADC deficiency is caused by mutations in the *DDC* gene, which result in a deficit of the AADC enzyme.[4] This then results in deficits in the neurotransmitters of dopamine, serotonin, norepinephrine and epinephrine.[5] There are over 50 genetic variants (genotypes) that can cause the disease.[5] Clinical expert advice to the EAG is that it is not fully known yet if genotype impacts on disease course or response to treatment.

2.2.1.1 Prevalence

The CS states that there is currently an estimated 853 people living with AADC deficiency in the European Union (including the United Kingdom (UK)). The CS also states that there are currently nine known people with the condition in the UK. The clinical expert consulted by the EAG, to whom nearly all AADC deficiency cases in the UK are referred, estimates that there is a maximum of 10 to 12 people with AADC deficiency.

The CS does not discuss the prevalence of AADC deficiency by ethnicity. We note that the condition is more prevalent in Asian populations, particularly people of Taiwanese and Japanese descent.[5] This is due to the presence of a founder variant in these populations.[5] All the clinical trials included as efficacy evidence for eladocagene exuparvovec in the CS were conducted in Taiwan (as stated in CS section B.3.15). All the participants except one were of Asian ethnicity and all had the founder mutation (IVS6+4A>T) (CS section B.2.3.1) (please see section 3.2.1.7 for a discussion about this).

2.2.1.2 Symptoms

As also noted in the CS, AADC deficiency symptom onset usually occurs in the first few months of life, with a mean age of diagnosis of 3.5 years (but this has ranged from 2 months to 23 years).[5] As the CS describes, people present with a range of symptoms, including hypotonia, dystonia, floppiness, behavioural and sleep difficulties, and delayed cognitive, motor and speech development. Oculogyric crises are a key, distressing feature of the condition. These are seizure-like episodes, where people experience (usually) upward involuntary movement of the eye, spasms, tremors, agitation and biting of the tongue and lips that is involuntary (CS section B.1.3.3.3).

2.2.1.3 Phenotypes and course of the disease

Wassenberg et al. (2017)[5] note that the phenotypic spectrum (that is, severity) of AADC deficiency is broad, and can range from mild to severe. As noted in the CS, around 80% of people with the condition are considered to have the severe phenotype.[5] People with the severe phenotype are the focus of the CS. The company define the severe phenotype as a person having “no or poor head control at 24 months of age” (CS section B.1.3.2). Our clinical expert agreed that this definition is reasonable. The CS (section B.1.3.3.2) states people with the severe phenotype “are bedridden all their lives, with complete dependence on their carer … [and] many patients will never achieve any motor milestones at any point throughout their lives”. Wassenberg et al. (2017)[5] state that people with severe disease are characterised by no or very limited developmental milestones achievement. Our expert stated that people with the severe form of the condition do not achieve full head control during their lifetime, though some may achieve partial head control and other motor milestones such as rolling and supported sitting. Our clinical expert agreed with the company’s description that people will be completely dependent on their carers, but she believed that “bedridden” was an extreme phrase to use to describe the lives of people with AADC deficiency. She noted that people can get around in wheelchairs or pushchairs. We note that people with AADC do not generally show a deterioration in their symptoms over

time.[5] Furthermore, our expert stated that in fact many do make limited developmental progress. We note that if people with AADC deficiency show a decline in their motor function, this can be due to secondary factors.[5]

2.2.1.4 Mortality

Our clinical expert informed us that around 10% of children with AADC deficiency die in infancy. After this, many survive into childhood and then in adolescence there is an increased risk of death.

2.2.1.5 Current treatments

The CS accurately states that there are no United Kingdom (UK) clinical guidelines for the management of AADC deficiency, including any published by NICE (CS section B.1.3.8.1). The CS (section B.1.3.8.1) notes that there is a consensus guideline for the diagnosis and treatment of AADC deficiency created by the International Working Group on Neurotransmitter Related Disorders (iNTD) and patient representatives.[5] The EAG's clinical expert (who co-authored the guideline) informed us that it is closely followed in practice.

As described in the CS, the current treatment approach to AADC deficiency is the management of symptoms through drug therapy and a multi-disciplinary team of specialists (CS section B.1.3.8). The CS states that disease-modifying treatments for AADC deficiency are not currently available (CS section B.1.3.8.1). The EAG's clinical expert mentioned that there is another gene therapy approach which has been undergoing trial and which has a different target to eladocagene exuparvovec. This approach is AAV2-hAADC delivery to the midbrain substantia nigra pars compacta and the ventral tegmental area regions .[6] Our expert stated that some families of the people she treats have elected to pay for this other gene therapy. Our expert is not aware of any other disease-modifying treatments or gene therapies that are undergoing trial. Our expert confirmed that no disease-modifying treatments (that is, no 'AADC deficiency precision therapies') are used in the NHS. She noted that the dopaminergic medications used to treat people with AADC deficiency (see below) result in some limited clinical improvement in some patients.

The CS describes the current approach to treating symptoms as "best supportive care" (CS section B.1.3.8.1). The current treatment approach outlined in CS section B.1.3.8.1 is in line with the approach that the EAG's clinical expert stated is used in clinical practice. Our expert stated people are started on a B6 medication such as pyridoxine or pyridoxal phosphate to boost any residual AADC enzyme (if there is any). People are then given a monoamine

oxidase inhibitor (MAOI). A dopamine agonist is also added to counteract the deficiency in dopamine. Other medications that are used are: folinic acid, adjunct tonal medications, melatonin (which is often needed) and rescue medications for oculogyric crises. Physiotherapy is given to strengthen core muscles, occupational therapy addresses hand movement/adaptations and speech and language therapy is used to address swallow safety and communication. People also require dietetic and dental support, as well as hip and spine surveillance, and vision and hearing monitoring. Genetic counselling is available for parents planning to have further children. Parents and carers are also taught how to manage oculogyric crises. Treatment is variable from child to child, especially the choice of type of dopamine agonist to use.

The CS states (section B.1.3.8.2) that the current approach to managing symptoms in people with AADC deficiency "very rarely helps patients with severe AADC deficiency achieve any motor milestones". Our clinical expert indicated that it is difficult to determine the impact of current care. She notes that some people who have severe disease but are at the 'milder' end of the severe spectrum do achieve motor milestones, but that there is limited progress. She also notes that the dopaminergic medications can sometimes help reduce the severity and frequency of oculogyric crises. The CS (section B.1.3.8.3) states that there is a clinical need for disease-modifying therapies that address the genetic cause of AADC deficiency. The EAG's clinical expert agrees with this. Our expert believes that established clinical management is less effective than gene therapies. She said that some children do not respond to dopaminergic medicines, and those who do respond often have limited response with regard to oculogyric crisis improvement or motor gains.

Overall, the EAG considers that the CS provides an accurate description of the current treatment of AADC deficiency. The EAG agrees there is a clinical need for disease-modifying treatments in the NHS.

2.2.2 Background information on eladocagene exuparvovec

The company describe eladocagene exuparvovec in CS sections B.1.2 and B.1.3.9. Eladocagene exuparvovec is a gene replacement therapy which delivers a copy of the *DDC* gene directly into the putamen area of the brain, and which is then expected to restore production of the AADC enzyme and, consequently, also the production of dopamine. Restoration of the production of dopamine is then anticipated to improve AADC deficiency symptoms, including motor function. The CS states that eladocagene exuparvovec delivers a full copy of the *DDC* gene, and, because of this, the underlying genetic mutation causing the

AADC deficiency is not anticipated to impact eladocagene exuparvovec's effectiveness (CS section B.1.3.9). The EAG's clinical expert agreed that this is reasonable.

Eladocagene exuparvovec is administered as a single dose in one surgery session. People receive a total dose of $1.8x10^{11}$ vector genomes (vg) infused into two sites of each putamen (meaning four 0.08 ML ($0.45x10^{11}$ vg) infusions are given) (CS Table 2). It is not expected that people will receive any further treatment with eladocagene exuparvovec after this first, one-off surgery (CS section B.1.2.3).

The CS states that the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) regulatory opinion is due in [redacted] (CS Table 2). The UK marketing authorisation is expected in [redacted]. We note that on 19th May 2022, the CHMP provided a positive opinion for eladocagene exuparvovec, recommending the granting of a marketing authorisation under exceptional circumstances (the latter means it is granted subject to specific obligations that will be subsequently reviewed).[7]

In line with the draft summary of product characteristics (SmPC), the CS states that eladocagene exuparvovec is indicated for [redacted]. As is also stated in the CS, the draft SmPC specifies that eladocagene exuparvovec should be administered [redacted] (p. 2).

The CS details the additional tests, investigations and resources that are expected to be needed as a result of introducing eladocagene exuparvovec into practice (CS Table 2). We provide a full critique of the additional resources required later in this report (in section 4.2.8). Briefly, our expert's opinion on the resources needed differs in some respects to the company's resource use included in their economic model base case.

The EAG believes that the company has provided an accurate description of eladocagene exuparvovec. However, there were differences in opinion between the EAG's clinical expert and the CS on the additional tests and investigations that will be required for the provision of eladocagene exuparvovec in practice. We discuss these differences further, and the implications for the economic evaluation, in section 4.2.8.

2.2.3 The position of eladocagene exuparvovec in the treatment pathway

The company describes the expected position of eladocagene exuparvovec in the care pathway for people with AADC deficiency in CS section B.1.3.10.1. The company state it will be the first intervention to target the underlying cause of the condition and they suggest eladocagene exuparvovec will become the standard of care. Our expert notes that eladocagene exuparvovec could become the standard of care, but that there are other gene therapies in development that could also become a standard of care. The company state eladocagene exuparvovec will be delivered at one to two specialised centre(s). The CS states that it is unclear what impact use of eladocagene exuparvovec will have on the use of the symptomatic treatments that form best supportive care, but that it is expected that people will still receive treatments based on their needs following administration of eladocagene exuparvovec. Our expert agrees with this. She notes some patients will need to maintain certain medications and that physiotherapy will be particularly important. The company's economic evaluation base case assumes that people will continue to receive best supportive care treatments as appropriate to their symptoms (CS section B.3.5.2.1).

CS sections B.1.3.10.1 and B.1.3.10.2 state that it is expected that all people in the UK who have AADC deficiency will be assessed for eligibility to receive eladocagene exuparvovec, as per the marketing authorisation. In CS section B.1.3.1, the company state there are nine known UK patients, yet CS section B.3.16 states that clinical experts estimate that [redacted] is currently eligible for the therapy. It is unclear from the CS why the other known UK patients would not be eligible. In clarification response A2, the company stated that the remaining known patients would not be eligible due to [redacted] having already received a gene therapy that restores AADC enzyme functioning and due to [redacted] having a mild phenotype. CS section B.3.16 states that over the next five years, clinical experts expect that there will be [redacted] for the treatment per year. The EAG's clinical expert suggests that all patients who meet the licenced indication, whose families are supportive of them receiving the treatment and who meet general anaesthetic and surgical safety requirements, will receive eladocagene exuparvovec (see section **Error! Reference source not found.** for details of the draft SmPC indication). She notes that not every patient or family will want to go through treatment, but most will. Our expert estimates that one to two of her existing patients may be treated with it and she also expects one to two new patients to be treated with it each year. Thus, the EAG's clinical expert's estimations of the number of people with AADC deficiency who might receive treatment with eladocagene exuparvovec differ marginally to the company's estimations.

EAG comment

The company's positioning of eladocagene exuparvovec in the clinical care pathway for AADC deficiency as a disease-modifying treatment, for people who match the proposed licenced indication, is appropriate. The company's expectation that people will likely continue to receive best supportive care, based on individual needs, after receipt of eladocagene exuparvovec, is also appropriate. The EAG's clinical expert provided marginally different estimations of the number of existing and new people with AADC deficiency expected to be treated with eladocagene exuparvovec to those stated in the CS.

2.3 Critique of the company's definition of the decision problem

Table 5 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE. The EAG considers that the decision problem appropriately matches the NICE scope. We note, however, that the company has not included data on the NICE scope-specified outcome of carer quality of life in the CS, despite this being measured in the clinical trials included in the CS (see section 3.2 for details of the included studies). The results are available, however, in a publication referenced in the CS, which reports results from the trials.[1] The company also did not address the NICE scope outcome of patients' HRQoL. We asked the company to confirm whether or not patients' health-related quality of life (HRQoL) was measured in the trials included in the CS and they confirmed it was not (clarification response A14).

Table 5 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People with aromatic L-amino acid decarboxylase (AADC) deficiency	Patients [redacted].	The population aligns with the anticipated EMA and MHRA marketing authorisation.	The company's decision problem population matches that specified in the draft SmPC and is therefore appropriate.
Intervention	Eladocagene exuparvovec	Eladocagene exuparvovec	N/A	The specified intervention is appropriate.
Comparators	Established clinical management without eladocagene exuparvovec	Best supportive care without eladocagene exuparvovec.	In line with the final scope, but with minor wording change.	The company's wording of the comparator differs to that in the NICE scope. In clarification response A1, the company confirmed that the two terms have the same meaning regarding the types of treatment, support and care people with AADC deficiency receive. The EAG therefore considers that the comparator reflects the NICE scope.
Outcomes	• motor function (including, where applicable, age-appropriate motor	All outcomes listed in the final NICE scope are included in the submission.	N/A	The company has provided trial results in the CS for all the outcomes specified in the NICE scope, except patients' and carers' health-related quality of life. The CS Executive Summary states carer quality of life data were collected, and we note trial results are available in a publication referenced in the CS.[1]

	milestones such as sitting, standing, walking) • autonomic nervous system functioning • speech and language development • cognitive development • body weight • oculogyric crisis • changes in levels of neurotransmitter metabolites in the cerebral spinal fluid • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)			
Economic analysis	Value for money: • Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes (PASs) and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	In line with NICE scope. A patient access scheme has been approved and is included within this submission.	N/A	The company presents a cost-effectiveness analysis in the CS using incremental cost per quality-adjusted life year. Details of the approved PAS are available in CS Table 2. The PAS discount is applied in the economic analyses. Resource use associated with using eladocagene exuparvovec is detailed in CS section B.3.5.1.
Subgroups	None specified	No subgroups are considered.	Limited sample size due to ultra-rare disease means data available for intervention and comparator is insufficient to allow for subgroup analyses.	No subgroup analyses are presented in the CS. The EAG agrees this is appropriate, given that none were specified in the NICE scope and given the limitations of the included trials' sample sizes.

Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.	In line with NICE scope.	N/A	All the issues specified in the NICE scope are discussed in CS section B.3.13.
Special considerations including issues related to equity or equality	None specified	In line with NICE scope.	N/A	The EAG has not identified any equity or equality issues. Our expert notes that only centres with the correct surgical and neurology expertise will be able to administer this treatment.

Source: NICE final scope and CS Table 1. This table partly reproduces CS Table 1. AADC, aromatic L-amino acid decarboxylase; CS, company submission; EAG, External Assessment Group; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; N/A, not applicable; NICE, National Institute for Health and Care Excellence; PAS(s), patient access scheme(s); SmPC, summary of product characteristics.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company used generally appropriate methods in their systematic literature review (Table 6). Despite some concerns with the literature searching methods (see Appendix 1 Table 53) and after clarification of the search date (clarification response A3), the EAG believe that the literature searches will have found all relevant studies.

With regards to the other aspects of the company's review, the study selection and data extraction processes were carried out well, and the methods of quality assessment were adequate. Table 6 summarises the methods and Table 54 in Appendix 2 provides the rationales for the EAG's responses in Table 6.

Table 6 Summary of EAG appraisal of systematic review methods

Systematic review components and processes	EAG response
Was the review question clearly defined using the PICOD framework or an alternative?	Yes
Were appropriate sources of literature searched?	Yes
Was the date coverage of the searches appropriate?	Yes
Were appropriate search terms used and combined correctly?	Mostly
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes
Were study selection criteria applied by two or more reviewers independently?	Yes
Was data extraction performed by two or more reviewers independently?	No
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes – with some overlap and one exception
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No
Is sufficient detail on the individual studies presented?	Yes
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review identified and included three open-label, single-arm, non-comparative trials assessing the efficacy and safety of eladocagene exuparvovec (CS section B.2.2):

- AADC-010 (phase I/II trial): NCT01395641[8]
- AADC-011 (phase II trial): NCT02926066[9]
- AADC-CU/1601: Compassionate use study[10]

All three trials were funded by the AADC Research Fund at National Taiwan University Hospital and the National Research Program for Biopharmaceuticals. The studies were funded in part by the company (PTC Therapeutics).[1]

The company provided the trial CSRs with the CS.[8-10] These were used as the primary data sources for the CS, with additional information from 23 publications of these studies (see CS Table 97). As stated in CS section B.2.2, the company provided a draft version of the AADC-011 study CSR. At the clarification questions stage of the appraisal, the company confirmed that the final CSR is not available yet (clarification response C3). The CS states the final CSR will contain additional analyses conducted as part of the EMA regulatory process (CS section B.2.11). It is not clear from the CS what additional analyses will be in the final CSR. In CS section B.2.11, the company states that no further data are expected from any of the studies, except for the updated CSR for AADC-011.

Data from all three trials are used in the company's economic model base case to inform estimates of the impact of eladocagene exuparvovec on motor function (see section 3.2.1.4 for more detail). Adverse event data from the trials were also used in the model.

3.2.1.1 Study characteristics

The CS details the characteristics and methodology of the three eladocagene exuparvovec studies in CS Table 5 to 8 in CS section B.2.2, and in CS section B.2.3. We have summarised the studies in Table 7. As stated in section 2.2, all three trials were conducted in Taiwan. The trials had a collective sample size of 30 enrolled participants. As stated in section 3.2.1, the studies were single arm, so there was no comparator. The company

addresses the comparator element of their decision problem and NICE scope through analysing the efficacy of best supportive care among individuals with AADC deficiency identified from the literature (see section 3.3).

Table 7 Characteristics of the three eladocagene exuparvovec trials

Study, country, n	Population	Intervention, dose (n receiving dose)	Primary outcome [a]	Length of follow-up
AADC-010 Taiwan n = 10	Children diagnosed with AADC deficiency, aged ≥2 years or with a head circumference large enough for surgery (clarification response A6)	Eladocagene exuparvovec, $1.8x10^{11}$ vg (n=10)	Proportion of participants achieving the following motor milestones [b]: • Full head control • Sitting unassisted • Standing with support • Walking with assistance	5 years+ (See Table 8 for details)
AADC-011 Taiwan n = 12	Children diagnosed with AADC deficiency, aged 2-6 years or with a head circumference large enough for surgery (clarification response A6)	Eladocagene exuparvovec, one of two doses: • $1.8x10^{11}$ vg (n = 3) [c] • $2.4x10^{11}$ vg (n = 9) [d]		1 year+ (See Table 8 for details)
AADC-CU/1601 [e] Taiwan n = 8	Children aged ≥2 years with diagnosed AADC deficiency	Eladocagene exuparvovec, $1.8×10^{11}$ vg (n=8)		5 years+ (See Table 8 for details)

Source: CS Tables 5 to 11.
[a] See CS Tables 5, 6, 7 and 8 for a list of the secondary outcomes.
[b] The milestones were assessed by one item each from the PDMS-2.
[c] Given to participants aged ≥ 3 years.
[d] Given to participants aged < 3 years.
[e] Retrospective observational study.

3.2.1.2 Overview of populations

The participant populations in the eladocagene exuparvovec studies match the population [redacted] (CS Executive Summary and CS Tables 9 to 11). The CS Executive Summary confirms that 28 participants had a diagnosis of severe AADC deficiency. It is unclear if the other two enrolled participants also had the severe phenotype. The participant eligibility criteria for the trials provided in CS Tables 9 to 12 do not appear to list a requirement for participants to have a severe phenotype. We note that the clinical effectiveness results in CS section B.2.6 show that participants had achieved none of the primary outcome motor milestones (full head

control, sitting unassisted, standing with support and walking with assistance) or additional motor milestones presented at baseline in any of the three studies, other than newly emerging or mastery of partial head control ([redacted] participants in AADC-010 and [redacted] participants in AADC-011). This is reflective of the company's definition of the severe phenotype used in the CS (that is "no or poor head control by the age of two", CS section B.2.9.3). As stated in section 2.2.1, our expert agreed the company's definition was a reasonable one.

3.2.1.3 Eladocagene exuparvovec doses

Studies AADC-010 and AADC-CU/1601 used [redacted]. In study AADC-011, three participants received the [redacted], and nine received a higher dose of $2.4x10^{11}$ vg, [redacted]. The company acknowledges this in CS section B.2.2. The company states that the "EMA considered the two doses to be equivalent in terms of safety and efficacy" (CS section B.2.2). We note, [redacted]. Clinical expert advice to the EAG is that combining the results from both doses is reasonable. The EAG therefore suggests this approach is appropriate.

3.2.1.4 Overview of primary outcome

The primary outcome in all three studies were the proportions of participants achieving the motor milestones of full head control, sitting unassisted, standing with support and walking with assistance. Clinical expert feedback to the EAG is that these are important outcomes, along with the impact of the gene therapy on oculogyric crisis episodes (also measured in the eladocagene exuparvovec studies; see section 3.2.3 for a further discussion about how the outcomes were measured and defined in the studies). Achievement of the motor milestones was measured by a motor function scale called the PDMS-2. Each motor milestone was measured using one item each from the scale (clarification response A11). The clinical expert advising the EAG commented that the way the motor milestones were defined in the trials is reflective of how they are assessed in practice (see CS Table 5 for definitions). She noted that motor function is not usually formally assessed using scales in practice; clinician judgement is used. The observed motor milestone achievement results are used in a scenario analysis in the company's economic model (CS Table 76). In the company's base case, participants' motor milestone development was predicted using a Bayesian growth model, rather than using motor milestones achievement results directly observed in the trials (CS section B.3.3). See section **Error! Reference source not found.**

for the EAG's critique of this approach. The EAG's preferred approach is to use the observed data and we have used this in our base case.

3.2.1.5 Participant follow-up

Table 8 shows the number of participants assessed at each follow-up timepoint in the three eladocagene exuparvovec studies. One participant was withdrawn in study AADC-010 and two were lost to follow-up between months 12 and 24 in study AADC-CU/1601 (see Table 8 for reasons). The company's economic model base case uses data from 28 of the participants. It is unclear to the EAG why data from the other two enrolled participants were not used.

The EAG found that the numbers of participants stated in the CS to have completed the longest follow-up timepoint in each study (60 months or more in AADC-010, up to 12 months in AADC-011 and up to 60 months in AADC-CU/1601) lacked clarity due to discrepancies in stated numbers between CS Tables 9 to 11, the clinical efficacy results presented in CS section B.2.6 and the company's clarification response (as shown in Table 8 and the accompanying footnotes below). The EAG therefore checked the numbers against the information available in the CSRs. Based on this check, it appears that the following numbers of participants had data available to inform the '60 month' results for studies AADC-010 and AADC-CU/1601 and '12 month' results for study AADC-011:

- AADC-010: [redacted] (assuming that 48 to < 60-month data was included in the '60 month' assessment, along with the ≥ 60-month data; this is unclear to the EAG). This is in line with the number of participants stated to be followed-up at Month 60 in CS Tables 14 and 15, which present results from the study.
- AADC-011: [redacted] (assuming that data at 9 to 12 months data was included in the '12 month' assessment, along with the ≥ 12-month data; this is unclear to the EAG). This is in line with the number of participants stated in the CSR results tables provided to the EAG in response to clarification question A19.
- AADC-CU/1601: [redacted] (as stated in the CS) (note clarification response A10 suggests [redacted]).

Given the discrepancies noted in Table 8, the EAG determined that at the '12 month' timepoint for study AADC-011, one participant is potentially unaccounted for in CS Document B. Two of the 12 enrolled participants could not attend an assessment, but results are presented for [redacted] participants in CS Document B rather than 10. We note, however, that results for all [redacted] participants are reported in the CSR. Inclusion of the participant missing from the CS makes the results for eladocagene exuparvovec [redacted] (see section 3.2.5.1), so this is not an issue.

The CS Executive Summary states that follow-up data beyond five years was available from the trials, but other than this brief statement and a brief summary of the results in the Executive Summary, the results were not presented in the CS. The CS references Tai et al. (2022)[1] for these data. We note Tai et al. (2022)[1] provides results for five participants with data available beyond five years in AADC-CU/1601, who attended voluntary follow-up visits. We asked the company at the clarification questions stage of the appraisal if any other long-term data were available. The company provided motor milestone achievement findings for a total of [redacted] participants in studies AADC-010 (n = [redacted]) and AADC-CU/1601 (n = [redacted]) at > 60 months, and [redacted] participants in study AADC-011 at > 12 months, from a January 2022 data cut (clarification response A21), as shown in Table 8. The > 60-month data are informative for verifying the assumptions made in the economic model about motor milestone achievement beyond five years after receiving eladocagene exuparvovec. We note, however, that it is unclear how participants progressed into the follow-up part of the studies (these appear to have been voluntary visits) and reasons for attrition during the longer-term follow-up. It is therefore unclear if those who were not followed-up or were lost to follow-up differed to those who were not in ways that may potentially bias the results.

Table 8 Number of participants followed-up at timepoints in the eladocagene exuparvovec studies

Study, baseline n	Timepoint				Number of participants withdrawn or lost to follow-up
	Up to 12 months	Up to 24 months	60 months	≥ 60 months; longest follow-up [a]	
AADC-010 n = 10	[redacted] ([redacted])	[redacted] ([redacted]) [b]	At 60 months or more: 5 (50%) [b c d]	[redacted]; [redacted] participant with data at 84 months	[redacted][8] – see footnote [g]
AADC-011 n = 12	CS Table 10 states no participants withdrew or were lost to follow-up [e]	[redacted] participants had data available beyond the 12-month trial period, including [redacted] participants with data at 60 months (clarification response A21; please note, at the factual accuracy check, the company stated they had reported this value in error and that [redacted] participant was followed up at			CS section B.2.3.1.3 notes that two participants were unable to attend the Month 12 follow-up due to

		60 months). Results were not included in the CS, but were provided in clarification response A21.			the COVID-19 pandemic
AADC-CU/1601 n = 8	[redacted]	[redacted]	Up to 60 months (voluntary visit): 6 (75%) [b f]	[redacted] participants with data at 120 months	2 lost to follow-up between months 24 and 60 (could not attend voluntary 60 months visit)

Source: CS Tables 9 to 11, CS Table 102, CS section B.2.3.1.3 and clarification response A21.
[a] Clarification response A21.
[b] Percentage calculated by the EAG.
[c] CS Table 14 suggests eight participants were followed up at the 60-month timepoint. [redacted]
[d] Clarification response A21 states that [redacted] participants had follow-up data beyond 60-months.
[e] CS Table 20 suggests [redacted] participants were followed up at 12-months. [redacted]
[f] Clarification response A10, Table 2, suggests that [redacted] participants were assessed at this timepoint rather than six.
[g] CS Table 9 states 1 withdrawn by investigator between months 12 and 24. Participant had influenza B and died due to encephalitis caused by influenza B. Influenza and death assessed as not related to eladocagene exuparvovec. This appears to be participant number 1007.[1] [redacted][8]
Tai et al. (2022) state this participant's 9 months data were used as 12 month data.[1] [redacted][8]

3.2.1.6 Ongoing studies and studies not identified in the CS

CS section B.2.11 states "*there are no ongoing studies…aside from the final CSR for AADC-011, no further data are expected for studies AADC-010, AADC-011, or AADC-CU/1601*." However, the EAG note in the decision problem form, two ongoing studies were specified, one of which is registered on clinicaltrials.gov. Brief details of these two studies are given below:

- [redacted] (The information about this study stated here was obtained from the company's decision problem meeting form and notes taken by the EAG during the decision problem meeting.)
- [redacted] (NCT04903288, N=2) is an open-label single arm study of the SmartFlow® MR compatible ventricular cannula for administering eladocagene exuparvovec to paediatric with genetically confirmed AADC deficiency. The trial consists of two phases: a trial phase concerning the safety of the cannula, and an extension phase, which will capture additional outcomes, including changes in motor

development, AADC-specific symptoms, and other pharmacodynamic measures. At the decision problem meeting on 24th February 2022, [redacted].

The EAG searched for other ongoing studies. Through the JPRN Search Portal, EAG additionally identified three studies (jRCT2033210641, jRCTs033180309 and UMIN000017802) conducted in Japan that evaluated the efficacy and/or safety of AAV-hAADC-2 administered into the putamen. A publication of the results related to these studies (Kojima et al., 2019)[11] states AAV-hAADC-2 is a similar AADC-expressing AAV vector to that used in the eladocagene exuparvovec studies. The EAG assumes that this means that it is not the same, but this is unclear. If it is the same vector, then results reported in this publication, which includes data for five people with the severe phenotype, may be relevant to this appraisal. The Kojima et al. (2019) [11] is not listed as an included or excluded study in CS appendix D.1.17, so it does not appear to have been identified by the company's searches.

The EAG is aware of one other study of eladocagene exuparvovec not included in the CS, which was presented at two conferences that took place close to the company's update searches date and after the update searches, respectively. We identified this study through our clinical expert, who told us she is aware of conference presentations on the compassionate use of eladocagene exuparvovec in people with AADC deficiency with different genotypes to participants included in the company's trials (who all had the founder mutation; see section 3.2.1.7). The EAG's expert believed these data were presented at the 7th International Symposium on Paediatric Movement Disorders on 9th to 11th February 2022 and the 14th European Paediatric Neurology Society Congress conference on 28th April to 2nd May 2022. The EAG has checked conference abstracts from these meetings and note that data is available on two people with AADC deficiency who were treated with eladocagene exuparvovec from a study published by authors located in France.[12,13] Brief, narrative efficacy and safety results are available in the abstract. The participants' genotype is not reported in the abstracts.

3.2.1.7 Patients' baseline characteristics

The EAG notes patient baseline characteristics are similar across the three trials, however there are minor exceptions for the AADC-011 trial (CS Table 12). Patients in AADC-011 are slightly younger at baseline: mean 31.3 months (SD 15.65) compared to 52.50 months (SD

30.84) and 58.80 months (SD 24.84) in AADC-010 and AADC-CU/1601 respectively, although the age range is similar and age at diagnosis is similar. Height and weight were not reported for the AADC-011 trial. Patients in the AADC-011 trial appear to have a higher mean PDMS-2 score for motor function than participants in the other two studies, although it looks like this may be due to an outlier because although the maximum score is high the median score ([redacted]) is similar to that in the AADC-010 study ([redacted]) (median score not reported for the AADC-CU/1601 study). The clinical expert to the EAG confirmed that the age ranges and sex ratio are similar to the patients they see in UK practice. They could not confirm the weight and height characteristics as their centre works in percentiles and not kilograms or centimetres, nor confirm motor scores as their centre does not use the PDMS-2 scoring system. Despite the slight age difference between trials, all trial patients are reflective of a severe AADC deficiency population in Asia: as stated in section 2.2.1, all the trials were conducted in Taiwan, all the patients except one were Asian, and all had the founder mutation.

The main difference between the trial populations and the AADC-deficiency population treated in England is race, and linked to this, the genotype. All patients in the company trials had the founder mutation which is prevalent in east Asian patients with the disease. Whereas our clinical expert explained that none of their patients in the UK (including those referred from Europe) had the founder mutation. They instead have a broad range of genotypes across a mainly White, European, and Pakistani population. This is in direct contrast to the statement in CS B.2.3.1.1 that "*most patients with AADC deficiency in the UK have the founder mutation".*

The consensus guidelines state that clear genotype/phenotype correlations could not be established, except that people with the founder variant identified in the consensus guidelines data all had a severe phenotype except for two sisters with the compound heterozygous variants that were clinically mild to moderate.[5] So in most cases the genotype has not been shown to affect the phenotype except for the founder mutation which is the mutation carried by all the patients in the company trials. The gene therapy delivers a complete copy of the missing AADC gene and is not specific to any genetic mutation, so theoretically the genotype should not matter, although this has not been tested in the trials. The EAG's clinical expert suggested that ideally the gene therapy should be tested on a broad spectrum of AADC genotypes.

EAG comment on included studies

The company included three single arm studies of eladocagene exuparvovec in the CS. The trials' populations and the doses of eladocagene exuparvovec used adequately reflect the proposed licenced indication, even though nine participants in one study [redacted] (for the reasons discussed above, we do not believe that this is an issue). Although the trials were conducted in Taiwan, clinical expert advice to the EAG indicates that the participant characteristics across the trials were generally representative of the people with AADC deficiency seen in clinical practice. The only exceptions she noted were race and genotype. All the participants in the trials had the founder mutation. Our expert noted that there is no evidence currently available to indicate if genotype might impact on treatment outcomes, but that the gene therapy should ideally be tested in people with a range of AADC genotypes.

3.2.2 Risk of bias assessment

The company's assessment of the risk of bias and quality of the eladocagene exuparvovec trials is in CS section B.2.5. Details of the methods and results of the company's critical appraisal are in CS sections D.1.1.3, D.1.1.5, D.1.3 and D.1.4.

All three company trials are open-label, single-arm studies and as such are inherently biased as blinding is not possible and there is no comparator or control group. Additionally, CS section B.2.5 reports that the AADC-CU-1601 trial was retrospective. The CS states that a control arm was not possible due to ethical reasons (a placebo-control arm would be unethical and there is a high unmet treatment need) and the very rare nature of the condition (CS sections B.2.5, B.2.8 and B.3.15), but it does reduce the certainty of the results.

Quality assessments of the company trials were carried out according to the criteria suggested in the NICE guidance for companies on evidence submissions. These are an adapted version of the Critical Appraisal Skills Programme (CASP) checklist for cohort studies (with or without a control group).[14,15]

Table 9, Table 10 and Table 11 show EAG responses to the checklist items alongside the company's responses. Our and company's rationales for our assessments are provided in Appendix 3. We differ in judgement from the company only regarding the accuracy of outcome measures and the completeness of follow-up affecting the sample size (see Appendix 3 for the rationale for all the quality assessment judgements).

The accuracy of the measurement of the outcomes remains open to bias. Firstly, that lack of blinding is unavoidable in an open-label, single-arm trial (and due to ethics around sham surgery) and so the investigators performing assessments could potentially be biased in their interpretation of results. The outcome measures used by the company are standard, validated tools, and measurements were carried out per protocol, which does reduce the potential for bias. However, no centralised assessment or independent clinical verification was reported for the measurement of any of the outcomes which would further reduce any bias relating to knowledge of the intervention and assessment of outcomes.

The population sample sizes of each trial were small, also unavoidable due to the rarity of the condition. There was some attrition, with discrepancies within or between the CS and the CSRs in regard to the number of patients lost (see section **Error! Reference source not found.** and Table 55, Table 56 and Table 57), thus affecting completeness of follow-up. Results at 12 months in the AADC-011 trial are reported out of the [redacted] patients that presented for follow-up instead of out of 12 patients which would be the intent to treat (ITT) population. This affects the results when expressed as a proportion. For example, in CS section B.2.6.2.1 and CSR Table 9, [redacted] of patients are reported as achieving head control whereas if this was an ITT analysis, as per the other trial reports, it would be [redacted] patients which is a smaller proportion. This is relevant when comparing results across the three trials, e.g. CS section B.2.6.2.2 states milestone achievement is comparable to that observed in the other trials for the same timepoint suggesting further improvement can be expected in later years after treatment. Thus there is a reporting bias for the results of this trial which favours the intervention.

Generally we find the company trials to be good quality single-arm studies with the normal risk of bias that is associated with this study design. We suggest there is a risk of bias around accuracy of outcome measurements, completeness of follow-up, and reporting of results from the AADC-011 trial.

Table 9 AADC-CU/1601 trial critical appraisal

Study name: AADC-CU/1601: Compassionate use treatment with eladocagene exuparvovec patients with AADC deficiency		
Study question	**Company response (yes/no/not clear/N/A)**	**EAG response**
Was the cohort recruited in an acceptable way?	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Probably

Have the authors identified all important confounding factors?	Yes	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Yes
Was the follow-up of patients complete?	Yes	No
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	Yes

Source: partly reproduced from CS Table 105

Table 10 AADC-010 trial critical appraisal

Study name: AADC-010: A phase 1/2 clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC		
Study question	**Company response yes/no/not clear/N/A)**	**EAG response**
Was the cohort recruited in an acceptable way?	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Probably
Have the authors identified all important confounding factors?	Yes	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Yes
Was the follow-up of patients complete?	Yes	No
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	Yes

Source: partly reproduced from CS Table 106

Table 11 AADC-011 trial critical appraisal

Study name: AADC-011: A clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC - an expansion		
Study question	**Company response yes/no/not clear/N/A)**	**EAG response**
Was the cohort recruited in an acceptable way?	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Probably
Have the authors identified all important confounding factors?	Yes	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Yes
Was the follow-up of patients complete?	Yes	No
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	Yes

Source: partly reproduced from CS Table 107

3.2.3 Outcomes assessment

All outcomes included in the NICE scope were measured in the three pivotal eladocagene exuparvovec studies except health-related quality of life (HRQoL). As stated in section 2.3, patient HRQoL was not measured in any of the studies while caregiver HRQoL was measured retrospectively, in a subset of caregivers of patients who received eladocagene exuparvovec (CS section B.3.2.2.10, company clarification response A14 and A15, Tai et al., 2022)[1].

The trial protocols, CSRs and company clarification responses provide details on how the primary and secondary outcomes were measured in the three studies. Key outcome measures from the health economic or EAG clinical expert perspective are shown in Table 12. The remaining outcomes relevant to the decision problem and NICE scope are in Appendix 4 Table 58.

Table 12 List of key NICE scope and decision problem related outcomes reported in the three pivotal eladocagene exuparvovec trials

Endpoint	Outcome type	Outcome measures
Primary	Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking)	**Proportion of patients achieving mastery of the following key motor milestones measured using the Peabody developmental motor scales, 2nd edition (PDMS-2):** • Full head control[a] • Sitting unassisted[b] • Standing with support[c] • Walking with assistance[d] at 12 months (AADC-011)/ 60 months (AADC-010, AADC-1601)
Secondary	Motor function	**Proportion of patients with newly emerging or mastery of the following key motor milestones measured using the PDMS-2:** • Full head control[e] • Sitting unassisted[f] • Standing with support[g] • Walking with assistance[h] up to 12 months (AADC-011)/ 60 months (AADC-010, AADC-1601)
		Raw scores for the PDMS-2 total score[i] up to 12 months (AADC-011)/ 60 months (AADC-010, AADC-CU/1601)
		Raw scores for the PDMS-2 subscales[i] up to 12 months (AADC-011)/ 60 months (AADC-010,[j] AADC-CU/1601)
	Oculogyric crisis (OGC)	**Number of patients with OGC** [redacted] AADC-010, AADC-CU/1601) **Number of hours per week with OGC**

		up to [redacted](AADC-011)/ [redacted] (AADC-010 only)
	Mortality	Deaths recorded as part of adverse event procedures
	Adverse events	**All treatment emergent adverse events (TEAEs)** to end of study (AADC-011, AADC-010, AADC-CU/1601). Participants in study AADC-011 were asked if they consented to additional follow-up of AEs post 12-months (clarification response A18).
	Health-related quality-of-life (for patients and carers)	**World Health Organization Quality of Life (WHOQOL)-BREF Survey (Taiwan version)** Retrospective assessment of caregivers' HRQoL, only (AADC-011, AADC-010, AADC-CU/1601)

Sources: CS section 2.2.6.2.7; CS Tables 9, 10 and 11; Company clarification responses A8, A9, A10, A11, A12, A14, A15; AADC-010 CSR section 11.4.1.2.3; AADC-011 CSR section 11.4.2.3 and 11.4.2.4.

[a] Full head control: score of 2 (maximum score i.e., mastery) on Item #10 of the PDMS-2 stationary (gross motor) subscale
[b] Sitting unassisted: score of 2 (maximum score i.e., mastery) on Item #14 of the PDMS-2 stationary (gross motor) subscale
[c] Standing with support: score of 2 (maximum score i.e., mastery) on Item #28 of the PDMS-2 locomotion (gross motor) subscale,
[d] Walking assisted: score of 2 (maximum score i.e., mastery) on Item #34 of the PDMS-2 locomotion (gross motor) subscale
[e] Full head control: score of 1 or 2 on Item #10 of the PDMS-2 stationary (gross motor) subscale
[f] Sitting unassisted: score of 1 or 2 on Item #14 of the PDMS-2 stationary (gross motor) subscale
[g] Standing with support: score of 1 or 2 on Item #28 of the PDMS-2 locomotion (gross motor) subscale,
[h] Walking assisted: score of 1 or 2 on Item #34 of the PDMS-2 locomotion (gross motor) subscale
[i] Subscales included: visual-motor integration (fine motor), stationary (gross motor), object manipulation (gross motor), locomotion (gross motor), and grasping (fine motor) i.e. reflex subscale was not assessed.
[j] CS Figure 16 states 2 years whereas the identical figure in the CSR AADC-010 (Figure 3) states [redacted]

An additional outcome assessed in all three trials and reported in the CS, but not included in the NICE final scope, was change from baseline in putaminal-specific 6-[18F] fluorodopa - positron emission tomography (PET) results, which indicates AADC gene transduction and dopamine production (CS B.2.6.1.9. B.2.6.2.9 and B.2.6.3.9). This outcome was measured [redacted]; AADC-CU/1601 trial protocol section 6.4.4; AADC-010 and AADC-011 trial protocol sections 4.5).

Outcomes from the three trials informing the company's economic model were:

- PDMS-2 total score (the EAG believe this outcome was used to predict motor milestone achievement in the company's base case).

- The number of participants achieving the following motor milestones: full head control, sitting unassisted, standing with support, and walking with assistance. These outcomes were used in a company scenario analysis.
- Moderate and severe treatment emergent adverse events (TEAEs) affecting ≥ 20% of patients within the first 12 months of follow up.

Based on advice from our clinical expert, the EAG believes that it would have been more appropriate to use the four key motor milestone achievement data observed in the trials in the company's economic model base case. We use these data in our base case.

3.2.3.1 Efficacy outcome(s)

Overall, relevant valid instruments for measuring motor function (Peabody Developmental Motor Scales, second edition (PDMS-2); Alberta Infant Motor Scale (AIMS)), and cognitive, speech and language development (Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT); Bayley Scales of Infant Development, third edition (Bayley-III)) were used in all three studies.[16-20] The EAG note however that AIMS is for children 18 months or younger and should not be used to evaluate older children whose motor function remains at the infant level.[21]. Given that that the patients included in the three AADC deficiency studies were aged ≥ 19 months, caution should be used when interpreting results from these studies using this outcome measure.

[redacted] (AADC-CU/1601 CSR section 9.7.5.1, AADC-010 CSR section 8.2.1.2, AADC-011 CSR section 8.2, CS Table 5). [redacted] (AADC-010 CSR section 8.2.1.2). [redacted].

The PDMS-2 is a validated instrument used to measure motor skills and developmental achievement in infants and young children.[16,19]Company clarification response A8 states it consists of six subscales, with a total of 249 items:

- Reflexes (8 items),

- Stationary (30 items),
- Locomotion (89 items),
- Object manipulation (24 items),
- Grasping (26 items),
- Visual motor integration (72 items).

Company clarification response A9 confirmed that “reflexes” subscale was not assessed in the three studies due to the nature of patients with AADC deficiency. Our clinical expert agreed that reflexes subscale is not relevant for assessing people with AADC deficiency. However, all other subscales were assessed and contribute to the total PDMS-2 score in the CS.

Scoring in each subscale is carried out as follows:

- Each item in a PDMS-2 subscale can be scored: ‘0’ (skill not met), ‘1’ (newly emerging), or ‘2’ (mastery),
- Within each subscale items are scored consecutively.
- When the child receives a score of three zeros in a row, the assessor can stop scoring that subscale, and move onto the next subscale

It should therefore be noted that while a higher PDMS-2 score indicates better motor function, the exact level of motor development cannot be determined by the total score because the subscale scores that contribute to the total score can vary (Company clarification response A8).

As shown in Table 13, the four key motor milestones assessed in the three eladocagene exuparvovec studies were:

- Full head control
- Sitting unassisted
- Standing with support
- Walking with assistance.

Each milestone was measured using one specific item of the PDMS-2 (see Table 13). The primary endpoint for all three trials was achieving ‘mastery’, i.e. a score of 2, for the relevant PDMS-2 item. However, the data used in the “naïve analysis” (i.e. the unadjusted, pooled outcome data; see section 3.2.6) of patients in the three eladocagene exuparvovec studies (CS Table 30) were the proportion of patients showing ‘newly emerging’ abilities or ‘mastery’, i.e. a score of 1 *or* 2, of these milestones (see Table 13; company clarification response A8 and A45).

Table 13 PDMS-2 key motor milestone items and scoring criteria

	Score Criteria	
PDMS-2 Key Motor Milestone	**1 (Newly Emerging)**	**2 (Mastery)**
Full head control (Stationary Item 10)	Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 seconds.	Sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds.
Sitting unassisted (Stationary Item 14)	Sitting without support and maintain balance while in a sitting position for 30 to 59 seconds.	Sitting without support and maintain balance while in a sitting position for 60 seconds.
Standing with support (Locomotion Item 28)	Taking 2 to 3 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk	Taking at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk.
Walking with assistance (Locomotion Item 34)	Walking at 4 to 7 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.	Walking at least 8 feet with alternating steps, with the examiner beside the patient and holding only one of the child's hands.

Our clinical expert stated that the PDMS-2 is not routinely used in clinical practice in the UK. Assessment of motor milestones is not usually based on a score. Assessment is carried out qualitatively, using clinician judgement. When evaluating motor function in practice, head control, rolling, sitting, standing and walking are assessed. Our expert stated that the eladocagene exuparvovec studies' primary outcomes of full head control, sitting unassisted, standing with support and walking with assistance are important, valid outcomes. Our expert agreed that the definitions of these outcomes used in the trials were reasonable and reflective of what clinicians look for in clinical practice. Our expert also thought it reasonable and clinically relevant to consider both 'newly emerging' skills and 'mastery' of key motor milestones.

[redacted] (AADC-CU/1601 trial protocol section 5.2.1, AADC-010 trial protocol section 4.5, AADC-011 trial protocol section 4.5). Company clarification response A16 confirmed that a single assessor trained in using the PDMS-2 performed all assessments in studies AADC-010 and AADC-011. This assessor and one other, also trained in using the PDMS-2, performed the assessments in AADC-CU/1601, with each patient evaluated by the same assessor for the duration of the study.

In agreement with CS section B.1.3.3.3, our clinical expert stated that in addition to motor function, the other key clinical outcome is oculogyric crises. Parents would like to see improvements in the duration, frequency and severity of oculogyric crises.
[redacted] (AADC-1601 trial protocol section 5.2.7).
[redacted] (AADC-010 trial protocol section 4.5).
[redacted]

3.2.3.2 HRQoL outcomes

The company confirmed that patient HRQoL was not measured in any of the three studies with the rationale that patients were “unable to communicate effectively due to being very young and having severe cognitive and language impairment.” (Company clarification response A14). Caregiver HRQoL was not assessed prospectively. However, it was assessed retrospectively in a subset of caregivers of patients in the company’s eladocagene exuparvovec studies (n=17) who completed the World Health Organisation (WHO)-BREF survey (Taiwanese version). The WHO-BREF survey is a cross-culturally valid assessment of quality of life.[22] It is a self-administered instrument, consisting of 26 items distributed among four domains (physical health, psychological health, social relationships and environment) and two additional items. When completing the WHO-BREF survey, caregivers were asked to evaluate their quality of life at the end of 2020 and to recall what their quality of life was like before their child underwent gene therapy with eladocagene exuparvovec.[1]

Results for this outcome are only reported in Tai et al. (2022; Company clarification response A15).

3.2.3.3 Safety outcomes

Across all three studies adverse events and serious adverse events were recorded, however there were differences in onset of monitoring and in the definition of serious adverse events.

The EAG note that in relation to serious adverse events, trial AADC-CU/1601 [redacted] (AADC-CU/1601 trial protocol section 5.2.20), while AADC-010 and AADC-011 trial protocol sections 10 refer to [redacted] The EAG believe that the reference to [redacted] may be an error in the translation of the protocol from Taiwanese to English, but in essence the three trials are using the same definition of serious adverse events.

The CS categorises the severity of adverse events as: mild, moderate or severe (CS Table 33) and the relatedness of adverse events to treatment as: unrelated, unlikely/remote, possible, probable and certain (CS Table 36).

EAG comment on outcomes assessment

Overall, we consider the efficacy, HRQoL and safety outcomes to be appropriate to the NICE scope and decision problem. Results for HRQoL are not reported in the CS and were not measured from the patient perspective. The company have provided a reasonable explanation as to why this is the case. Caregiver HRQoL was assessed retrospectively only, using a validated tool.

3.2.4 Statistical methods of the included studies

A summary and critique of the statistical methods used in studies AADC-CU/1601, AADC-010 and AADC-011 are presented in Table 14, below.

Table 14 Summary and EAG critique of the statistical methods used in the 3 eladocagene exuparvovec pivotal studies

Analysis populations
AADC-CU/1601, AADC-010 and AADC-011:

[redacted]. (AADC-CU/1601 and AADC-010 CSRs section 9.7.3, AADC-011 CSR section 11.1)

Safety population,
[redacted] (AADC-CU/1601, AADC-010, AADC-011 SAPs sections 2.2.2).

AADC-011: *"Not all subjects were able to return for follow-up visits, primarily due to the COVID-19 pandemic; as such, only 9 of the 12 enrolled subjects were assessed for the primary endpoint*" (CS section B.2.6.2.2).

EAG comment:
For all studies, the analysis populations for both efficacy and safety were to include all enrolled patients as all patients in each trial were treated with AAV2-hAADC gene therapy. However, in study AADC-011 the primary endpoint was actually analysed using the number of patients who had the outcome assessed for the primary endpoint as the denominator. This could bias the result toward favouring eladocagene exuparvovec.

Sample size calculations

AADC-CU/1601, AADC-010 and AADC-011:
[redacted] (AADC-CU/1601, AADC-010, AADC-011 CSRs sections 9.7.4).

AADC-CU/1601, AADC-010:
CS Table 13 reports a statistical power of 0.95 for each study but the CS provides no further details on when (*a-priori* or post-hoc) and how this was calculated

EAG comment:
Due to the apparently conflicting information in the CSRs and CS Table 13, it is unclear to the EAG whether a formal sample size was calculated for studies AADC-CU/1601 and AADC-010. The EAG also believes it is uncertain whether these two studies were sufficiently powered to detect statistically significant results.

Methods to account for multiplicity

AADC-1601 and AADC-010:
[redacted] (AADC-CU/1601, AADC-010 SAPs sections 4.2.1).

AADC-011:
[redacted] (AADC-011 SAP section 4.2.1).

EAG comment:
Appropriate procedures were followed in trials AADC-CU/1601 and AADC-010 to prevent statistically significant effects being detected by chance.

Analysis of outcomes
AADC-1601, AADC-010 and AADC-011: Primary efficacy analysis: [redacted] (AADC-CU/1601, AADC-010, AADC-011 SAPs sections 4.2.1). Secondary analyses: *PDMS-2, AIMS, Bayley-III, CDIIT* [redacted] (AADC-CU/1601, AADC-010, AADC-011 SAPs sections 4.2.2). *Neurotransmitter metabolites and body weight* [redacted] (AADC-CU/1601, AADC-010, AADC-011 SAPs sections 4.2.2 and 5.2). *Oculogyric crises episodes* [redacted] (AADC-CU/1601, AADC-010, AADC-011 SAPs sections 4.2.2). *Adverse events* Descriptive statistics (e.g. frequency, counts) were used.
EAG comment: Appropriate analytical methods were used.
Handling of missing data
[redacted] (AADC-CU/1601, AADC-010, AADC-011 SAPs sections 2.3). (NB. The LOCF approach was used to impute missing data in the pooled analysis of the three studies (see section 3.2.6).)
EAG comment: For the primary efficacy analysis this is essentially baseline carried forward as the patients do not have any key motor function. This is a conservative estimate.
Subgroup analyses
AADC-CU/1601 and AADC-010: [redacted] (AADC-CU/1601, AADC-010 SAPs sections 2.2.1). <u>AADC-011</u>

[redacted] (AADC-011 SAP 2.2.1).
EAG comment: The chosen subgroup analysis for AADC-011 is appropriate given that patients in this study could receive one of two different doses of eladocagene exuparvovec.
AIMS: Alberta Infant Motor Scale; Bayley III: Bayley Scales of Infant Development – Third Edition; CDIIT: the Comprehensive Developmental Inventory for Infants and Toddlers; PDMS-2: Peabody developmental motor scales, 2nd edition

EAG comment on study statistical methods

The EAG did not identify any issues with the statistical methods used in the three pivotal eladocagene exuparvovec studies, except for two issues. First, in the EAG's opinion, there is a lack of clarity around sample size calculation for studies AADC-CU/1601 and AADC-010, which means it is uncertain whether these two studies were sufficiently powered to detect statistically significant results. Second, that in study AADC-011 the primary endpoint (motor milestone achievement) was analysed using the number assessed for the outcome as the denominator rather than the number of participants at baseline. This biases the results in favour of eladocagene exuparvovec.

3.2.5 Efficacy results of the intervention studies

Below we summarise available results from the three eladocagene exuparvovec studies for the following motor milestones outcomes, as they were either the studies' primary outcomes or informed the company's economic model:

- The primary outcome of the proportion of participants achieving mastery of key motor milestones (clarification response A10).
- The proportion of participants achieving emerging skills on or mastery of key motor milestones (this outcome was used in the EAG base case and a company economic model scenario analysis).
- PDMS-2 total scores (which the EAG believes informed the company's economic model base case).

We also present results for the following key outcomes for parents/caregivers:

- oculogyric crises
- caregiver HRQoL

Please see CS section B.2.6 for the results for other outcomes specified in the NICE scope. We briefly summarise the results for the other clinical efficacy outcomes in section 3.2.5.5

3.2.5.1 Key motor milestones

The primary endpoint in all three trials was the proportion of patients achieving mastery of the following key motor milestones measured using the Peabody developmental motor scales, 2nd edition (PDMS-2): full head control, sitting unassisted, standing with support and walking with assistance. Data at baseline, 12 months, 24 months and 60 months were presented in the CS for AADC-CU/1601 (CS Table 25) and AADC-010 (CS Table 14). Data at 12 months only were presented for AADC-011 in CS Table 19. The EAG has noted that there are some discrepancies between the number of patients reported in the CS to be assessed (as outlined in section 3.2.1.5) or to have achieved a milestone compared to that reported in the relevant CSRs. The number and proportion achieving milestones in all three studies, and any discrepancies in numbers, are reported in Table 15 and Table 16 below. The EAG understands that the results in Table 15 and Table 16 show the number and proportion of participants among those who were assessed at each timepoint who showed achievement of a milestone at that point. The only exception to this, is for the 'emerging' and 'mastery' results combined for study AADC-CU/1601 which show the cumulative number and proportion of participants who achieved each milestone up to the relevant timepoint over the course of the trials. Please note that at the factual accuracy check stage of the appraisal, the company provided revised versions of Table 15 and Table 16, which included confirmation of which of the discrepant values were the correct ones to use (factual accuracy check Issues 10 and 11).

Table 15: Key motor milestone achievement (mastery, i.e. score of 2 on relevant PDMS-2 item) by timepoint

Motor milestone	Timepoint	AADC-CU/1601 (N=8)		AADC-010 (N=10)		AADC-011 (N=12)	
		No. assessed	No. patients (%)[a]	No. assessed	No. patients (%)[a]	No. assessed	No. patients (%)
No motor function	Baseline	8[b] or 5[c]	8 (100)	10	10 (100)	12	12 (100)
Full head control (PDMS-2 item #10)	Baseline	8[b] or 5[c]	0 (0)	10	[redacted]	12	0 (0)
	Month 12	8[d]	[redacted]	[redacted][e] or 10[f]	[redacted]	[redacted][g] or [redacted][h]	[redacted][o] or [redacted][h]
	Month 24	8[d]	[redacted]	9	[redacted]	[redacted][i]	NR[n]
	Month 60	7[d] or [redacted][k]	[redacted]	8	[redacted][f] or [redacted][e] ([redacted] or [redacted][k])	[redacted][j]	NR[n]
Sitting unassisted (PDMS-2 item #14)	Baseline	8[b] or 5[c]	0 (0)	10	[redacted]	12	0 (0)
	Month 12	8[d]	[redacted] (25)[l]	[redacted][e] or 10[f]	[redacted]	[redacted][g] or [redacted][h]	[redacted][o] or [redacted][h]
	Month 24	8[d]	[redacted]	9	[redacted]	[redacted][i]	NR[n]
	Month 60	7[d] or [redacted][k]	[redacted]	8	[redacted][f] or [redacted][e] ([redacted] or [redacted][k])	[redacted][j]	NR[n]
Standing with support (PDMS-2 item #28)	Baseline	8[b] or 5[c]	0 (0)	10	[redacted]	12	0 (0)
	Month 12	8[d]	[redacted]	[redacted][e] or 10[f]	[redacted]	[redacted][g] or [redacted][h]	[redacted]
	Month 24	8[d]	[redacted]	9	[redacted][m]	[redacted][i]	NR[n]
	Month 60	7[d] or [redacted][k]	[redacted]	8	[redacted]	[redacted][i]	NR[n]
Walking with assistance (PDMS-2 item #34)	Baseline	8[b] or 5[c]	0 (0)	10	[redacted]	12	0 (0)
	Month 12	8[d]	[redacted]	[redacted][e] or 10[f]	[redacted]	[redacted][g] or [redacted][h]	[redacted]
	Month 24	8[d]	[redacted]	9	[redacted]	[redacted][i]	NR[n]
	Month 60	7[d] or [redacted][j]	[redacted]	8	[redacted]	[redacted][i]	NR[n]

Sources: partly reproduced from CS Tables 14, 19 and 25
NR, not reported.
[a] % calculated on basis of denominator as the number of patients at baseline.
[b] CS section B.2.6.3.2
[c] Company clarification A10 Table 2
[d] Company clarification response A10 Table 2
[e] AADC-010 CSR Table 14.2.1.3

[f] CS Table 14
[g] CS Table19 and AADC-011 CSR Table 9. Note CS section B.2.6.2.2 "*Not all subjects were able to return for follow-up visits, primarily due to the COVID-19 pandemic; as such, only 9 of the 12 enrolled subjects were assessed for the primary endpoint*".
[h] AADC-011 CSR Table 14.2.1.3.3
[i] Company clarification A21
[j] AADC-CU/1601 CSR Data Table 1
[k] Calculated by the EAG.
[l] CS Table 25 states proportion of [redacted]; EAG calculates [redacted]5 (i.e. [redacted]), using baseline denominator
[m]CS Table 14 states [redacted]; EAG calculates [redacted], using the baseline denominator.
[n] Results up to 60 months are reported in clarification response A21, but exact numbers of participants achieving each motor milestone at each timepoint is not reported.
[o] There appears to be an error in the reporting of the %s in CS Table 19, which the EAG has corrected here.
Bold shows where there are discrepancies between numbers provided in sources or where the EAG's percentage calculations differ to those of the company's.

Table 16: Key motor milestone achievement (newly emerging or mastery i.e. score of 1 or 2 on relevant PDMS-2 item) by timepoint

Motor milestone	Timepoint	AADC-CU/1601 (N=8)		AADC-010 (N=10)		AADC-011 (N=12)	
		No. assessed	No. patients (%)[a]	No. assessed	No. patients (%)[a]	No. assessed	No. patients (%)
No motor function	Baseline	8	8 (100)	10	10 (100)	12	12 (100)
Full head control (PDMS-2 item #10)	Baseline	**8[b] or 5[c]**	[redacted]	[redacted]	[redacted]	12	0 (0)
	Month 12	8	[redacted]	[redacted]	[redacted]	**9[d] or [redacted][e]**	**6[d] or [redacted][e] (50 or 58)**
	Month 24	8	[redacted]	[redacted]	[redacted]	[redacted][f]	NR[g]
	Month 60	7	[redacted]	[redacted]	[redacted]	[redacted]	NR[g]
Sitting unassisted (PDMS-2 item #14)	Baseline	**8[b] or 5[c]**	[redacted]	[redacted]	[redacted]	12	0 (0)
	Month 12	8	[redacted]	[redacted]	[redacted]	**9[d] or [redacted][e]**	**3[d] or [redacted][e] (33 or 40)**
	Month 24	8	[redacted]	[redacted]	[redacted]	[redacted][f]	NR[g]
	Month 60	7	[redacted]	[redacted]	[redacted]	[redacted]	NR[g]
Standing with support (PDMS-2 item #28)	Baseline	**8[b] or 5[c]**	[redacted]	[redacted]	[redacted]	12	0 (0)
	Month 12	8	[redacted]	[redacted]	[redacted]	**9[d] or [redacted][e]**	0[d,e]
	Month 24	8	[redacted]	[redacted]	[redacted]	[redacted][f]	NR[g]
	Month 60	7	[redacted]	[redacted]	[redacted]	[redacted]	NR[g]
Walking with assistance (PDMS-2 item #34)	Baseline	**8[b] or 5[c]**	[redacted]	[redacted]	[redacted]	12	0 (0)
	Month 12	8	[redacted]	[redacted]	[redacted]	**9[d] or [redacted][e]**	0[d,e]
	Month 24	8	[redacted]	[redacted]	[redacted]	[redacted][f]	NR[g]
	Month 60	7	[redacted]	[redacted]	[redacted]	[redacted]	NR[g]

Sources: partly reproduced from company clarification A10 Table 1 and 2, AADC-010 CSR Table 14.2.1.3, CS Table 20, AADC-011 CSR Table 11, AADC-011 CSR Table 14.2.1.3.3.
NR, not reported.
[a] % calculated by the EAG on basis of denominator as the number of patients at baseline
[b] CS section B.2.6.3.2
[c] Company clarification A10 Table 2
[d] AADC-011 CSR Table 11 and CS Table 20.

[e] AADC-011 CSR Table 14.2.1.3.3
[f] Company clarification response A21
[g] Results up to 60 months are reported in clarification response A21, but exact numbers of participants achieving each motor milestone at each timepoint is not reported.
Bold shows where there are discrepancies between numbers provided in sources or where the EAG's percentage calculations differ to those of the company's.

At baseline, across all three studies, patients had no motor function in terms of the four key motor milestones (see Table 15). In terms of mastery of key motor milestones (i.e. a score of 2 on the relevant PDMS-2 item), data at 12 months were comparable across all three trials in that at least [redacted] in each trial had achieved mastery of the milestone of sitting unassisted. At 60 months at least [redacted] in trial AADC-CU/1601 and AADC-010 had achieved mastery of full head control and sitting unassisted (based on data reported in CS Table 14), and at least [redacted] mastery of standing with support. [redacted] in study AADC-010 also achieved mastery of walking with assistance at 60 months.

Newly emerging or mastery of the four key motor milestones was reported in the CS for studies AADC-010 (CS Table 15) and AADC-011 (CS Table 20). Additional data were also provided in the CSRs. For study AADC-CU/1601, the company provided data for this outcome in company clarification response A10. The number and proportion of participants with newly emerging or mastery of the four key motor milestones over time in the three studies, and any discrepancies in numbers between data sources, are reported in Table 16 below. At 12 months, in each of the three studies, at least [redacted] of patients had newly emerging or mastery of full head control. At 12 months [redacted] (study AADC-010) had newly emerging or mastery of standing with support. At 60 months, in studies AADC-CU/1601 and AADC-010, at least [redacted] had emerging or mastery of head control, [redacted] emerging or mastery of sitting unassisted, [redacted] emerging or mastery of standing with support and at least [redacted] emerging or mastery of walking with assistance.

The CS does not report data beyond 12 months for study AADC-011 and 60 months for studies AADC-CU/1601 and AADC-010. Company clarification response A21 provides some longer-term data, in narrative format only (data cut January 2022), for these three studies. In summary:

- AADC-010: [redacted] patients had follow up > 60 months (72 months, n=[redacted]; 84 months, n=[redacted]). [redacted] patients maintained their highest motor milestone. [redacted] patient, experienced improvement in motor function after intermittent loss of sitting unassisted due to hip dysplasia surgery.
- AADC-011: [redacted] patients had follow up > 12 months (30 months, n=[redacted]; 48 months, n=[redacted]; 60 months, n=[redacted]; information not reported for [redacted] patient). Compared to 12 months post-surgery, [redacted] patients improved their motor milestone attainment and [redacted] maintained their motor milestone attainment. Please note that at the factual accuracy check stage of the appraisal, the company identified that the numbers of participants stated to have been followed up at each timepoint were reported

erroneously in clarification response A21. The company clarifies the numbers followed up at each timepoint in factual accuracy check Issue 7. This does not affect the total number of participants followed up (n = [redacted]) nor the results reported above, which remain the same.

- In AADC-CU/1601: [redacted] patients had follow up > 60 months (72 months, n= [redacted]; 120 months, n= [redacted]). [redacted] patients maintained their highest motor milestone, with [redacted] patient maintaining an emerging attainment of their highest milestone.

3.2.5.2 PDMS-2 total score

Results for PDMS-2 total score were presented in CS sections B.2.6.1.3, B. 2.6.2.3 and 2.6.3.3. Additional data relating to LS means for change for baseline at various timepoints were also reported in the CSRs.

Improvements in PDMS-2 least squares mean change from baseline in PDMS-2 total scores for patients can be observed from 3 months, with considerable increases in the first 24 months (Table 17). There were statistically significant changes from the baseline at the Month 60 endpoint (studies AADC-CU/1601 and AADC-010; p<0.0001) and at Month 12 endpoint (study AADC-011; p<0.0001) (CS sections B.2.6.1.3, B.2.6.2.3 and B.2.6.3.3).

Table 17: Least Squares Means for Change from Baseline in PDMS-2 Total Score

Trial	AADC-CU/1601 (N=8)	AADC-010 (N=10)	AADC-011 (N=12)
Least squares (LS) mean for change from baseline (95% CI)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	Not reported
36 months	[redacted]	[redacted]	Not reported
48 months	[redacted]	[redacted]	Not reported
60 months	[redacted]	[redacted]	Not reported
Source: AADC-1601 CSR Supplemental Table 3; AADC-010 CSR Table 14.2.2.2; AADC-011 CSR Table 14.2.2.2.3			

Information on PDMS-2 total score beyond 60 months post-surgery was not reported in the CS. However, Tai et al. (2022)[1] provides information on five patients from study AADC-CU/1601 who had follow up greater than 60 months (range 6 to 10 years). Three of the patients were reported to have stable PDMS-2 scores. The remaining two patients

experienced decline in motor scores, three- and five-years post- surgery respectively, associated with non-gene therapy related events (knee growth plate injury due to infection before gene therapy; dystonic under training or examination). Corrective leg surgery seven years post-surgery reportedly stabilised motor function in one patient. The second patient received aquatic therapy to treat their dystonic symptoms, however the outcome on motor function was not reported.

3.2.5.3 Oculogyric crisis

As outlined in section 3.2.3 of this report, two studies assessed the number of patients with oculogyric crisis up to [redacted] (AADC-CU/1601 and AADC-010) and one up to [redacted] (AADC-011). Two studies (AADC-010 and AADC-011) measured the number of hours per week with oculogyric crisis up to [redacted], respectively.

The CS only reports data for the number of patients with oculogyric crisis up to [redacted] for study AADC-CU/1601 (CS figure 68). CSR section 11.4.2.6.1 highlights that [redacted]. [redacted] (CS Figure 68).

Table 18 reports summary statistics for time patients experienced oculogyric crisis in hours per week following eladocagene exuparvovec treatment in study AADC-010. This showed a gradual reduction in oculogyric crises in hours per week over time (with a reduction from baseline by a mean of [redacted] hours per week at 3 months (n=[redacted]), [redacted] hours per week at 6 months (N=[redacted]), [redacted] hours per week at 9 months (n=[redacted]), and [redacted] hours per week at 12 months (n=[redacted]).

Table 19 reports summary statistics for time patients experienced oculogyric crisis in hours per week following eladocagene exuparvovec treatment in study AADC-011. However, only data up to 3 months was reported. Oculogyric crisis activity reduced from baseline by [redacted] hours per week at 1 month (n=[redacted]), [redacted] hours per week at 2 months (n=[redacted]) and [redacted] (n = [redacted]) hours per week at month 3.

In regard to the number of hours per week with oculogyric crisis, results reported from trials AADC-010 and AADC-011 differed in the degree of reduction in the length of oculogyric crisis episodes they found at three months (see Table 18 and Table 19). Please note that at

the factual accuracy check stage of the appraisal, the company clarified that the data they had provided in the CS were incorrect and they thus provided a revised version of Table 18, with corrected values, in factual accuracy check Issue 16).

Table 18: AADC-010 - Summary statistics for time subjects experienced oculogyric crisis in hours per week following eladocagene exuparvovec treatment

Interval	Statistics	Observed Values	Change from baseline (Hours/Week)[a]
Baseline	n	[redacted]	-
	Mean (Std)	[redacted]	-
	Median	[redacted]	-
	Min, Max	[redacted]	-
Month 3	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 9	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Source: Reproduction of CS Table 16
[a] No p-values reported
[b] 10 patients were enrolled in study AADC-010
Max: maximum; Min: minimum; Std: standard deviation

Table 19: AADC-011 - Summary statistics for time eladocagene exuparvovec-treated subjects experienced oculogyric crisis in hours per week

Interval	Statistics	Observed Values (Hours/Week)	Change from Baseline (Hours/Week)
Baseline	n	12	-
	Mean (Std)	10.30 (1.820)	-
	Median	10.07	-
	Min, Max	7.81, 14.25	-
Month 1	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 2	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 3	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Source: Reproduction of CS Table 22
[a] No p-values reported
[b] 12 patients were enrolled in study AADC-011
Max: maximum; Min: minimum; Std: standard deviation

3.2.5.4 HRQoL outcomes

Patient HRQoL was not measured in any of the studies (company clarification A14). The company confirmed in company clarification A15 that caregiver HRQoL was assessed retrospectively in 17 caregivers of patients receiving eladocagene exuparvovec using the World Health Organization Quality of Life (WHOQOL)-BREF questionnaire. We note the Taiwan version was used.[1] Results were not reported in the CS but in an article by Tai et al., 2022.[1] Quality of life for caregivers statistically significant improved in all five domains: overall ($p < 0.001$), physical health ($p < 0.001$), psychological ($p < 0.001$), social relationship ($p = 0.006$), and environment ($p < 0.001$). There was only no statistically significant improvement on three of the 28 questions in the measure: sex life ($p = 0.069$), support from friends ($p = 0.096$), and transport ($p = 0.058$).[1]

3.2.5.5 Other efficacy outcomes

In regard to the other NICE scope and decision problem related efficacy outcomes reported in the 3 pivotal trials, improvements or statistically significant improvements from baseline to pre-defined endpoints were found for:

- motor function as measured by the Alberta Infant Motor Scale (AIMS) total score

- cognitive speech and language skills as measured by the CDIIT or Bayley III
- body weight
- levels of homovanillic acid (HVA; the metabolite of dopamine)

However, for 5-hydroxyindoleacetic acid (5-HIAA; the metabolite of serotonin), change from baseline at 12 months were inconsistent between trials with no change (AADC-CU/1601; CS section 2.6.3.8), an increase (AADC-010; CS section B2.6.1.8) and a decrease (AADC-011; CS section B.2.6.2.8) reported.

3.2.5.6 Safety outcomes

The safety data from the three company trials are pooled into one set of data representing 28 patients who received eladocagene exuparvovec therapy. The median duration of follow-up was [redacted] months (range [redacted] to [redacted] months), although only moderate-to-severe treatment adverse events occurring in ≥20% of patients up to month 12 following eladocagene exuparvovec treatment were included in the economic model (CS section B.3.4.4).

CS sections B.2.10 and B.2.12.3 report and summarise the adverse events. Note that the company are using the terms 'adverse event' and 'treatment emergent adverse event' interchangeably. There were [redacted] adverse events:

- [redacted] patients reported at least one adverse event and [redacted] patients had at least one serious adverse event.
- Most adverse events were mild: [redacted] were mild; [redacted] were moderate; and [redacted] were severe. There were [redacted] serious adverse events.
- Most of the common adverse events were associated with AADC deficiency symptoms:

Table 20 The most common adverse events occurring in ≥2 patients

Adverse event	Patients N (%)
Pyrexia	[redacted]
Dyskinesia	[redacted]
Upper respiratory infection	[redacted]
Gastroenteritis	[redacted]
Pneumonia	[redacted]
Upper gastrointestinal haemorrhage	[redacted]

Source: CS Table 32

- [redacted] deaths occurred, neither were considered to be treatment-related: [redacted] due to influenza B encephalitis after 12 months of follow-up and [redacted] due to complications of AADC deficiency outside the 60-month study period.

A low rate of TEAEs is reported:

- [redacted] out of [redacted] adverse events were considered possibly or likely related to treatment
- [redacted] adverse events were considered definitely related to treatment
- [redacted] treatment-related deaths
- Dyskinesia was the most frequent TEAE: [redacted]

The only treatment-related TEAE that occurred in [redacted] of patients is dyskinesia. The CS states this was expected due to the eladocagene exuparvovec therapy initiating the production of dopamine. Our expert agrees that this would be expected. She notes that this would be managed by: a reduction and weaning off of dopaminergic medications; carefully monitored sedation (e.g. benzodiazepines); low dose tetrabenazine if severe (this is rarely needed); and hospitalisation if needed (this rarely is needed).

The EAG notes that dyskinesia is also a symptom of AADC deficiency.

Data for moderate to severe TEAEs are used in the economic model due to their assumed impact on quality of life and associated costs (CS B.3.2.2.11):

- Four moderate to severe TEAEs occurred in [redacted] of patients within 12 months of eladocagene exuparvovec therapy: dyskinesia, pneumonia, gastrointestinal disorders and gastroenteritis (CS B.2.10.5.2). These are included in the economic model (CS B.3.2.2.11).

As stated in 2.2.2, the EAG notes that the CHMP summary of opinion published on 19th May 2022 is positive. It states that the most common side effects of eladocagene exuparvovec are initial insomnia, irritability and dyskinesia.[7] Irritability is reported in the CS as an adverse event affecting [redacted] of patients (CS Table 32), it was not the most common adverse event. Irritability is also a symptom of AADC deficiency.

3.2.6 Pooled analysis of eladocagene exuparvovec studies

The CS does not present a meta-analysis. The motor milestone achievement results from the three, single arm eladocagene exuparvovec trials were pooled, as presented in CS Table 30 (reproduced in this report in section 3.5). The table shows the motor milestones achieved

at baseline and each following year up to Year 5, and the corresponding proportion of participants who achieved a milestone as their highest motor milestone achievement at each timepoint for 28 of the 30 enrolled participants. The data in CS Table 30 were used in an economic model scenario analysis. By cross-referencing the results in the table to the company's economic model, the EAG identified that they are those when a last observation carried forward (LOCF) approach is used for estimating missing data. The EAG cannot check the accuracy of the pooled proportions of participants from each study achieving motor milestones. This is because the numerator and denominators are not provided in CS Table 30, the EAG does not have the individual participant data to be able to check the missing data imputation and the results are for the highest motor milestone achieved; data for which the EAG does not appear to have access.

Clarification response A45 confirmed that CS Table 30 shows the proportions of participants who were classed as showing either 'newly emerging' abilities or 'mastery' of the highest milestone achieved. Clinical expert advice to the EAG indicates that both 'newly emerging' and 'mastery' skills are clinically relevant. The EAG therefore considers that it is appropriate to combine the results for both categories of achievement and to use these in the economic model.

We use the participant motor milestones achievement distribution with missing data imputed using the LOCF approach in our EAG base case. We considered the LOCF method to be a reasonable assumption in the context of AADC deficiency treatment with eladocagene exuparvovec because:

- Clinical advice to the EAG is that, due eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time.
- The AADC treatment consensus guidelines[5] note that people with AADC deficiency generally do not show a deterioration in their symptoms over time.
- Long-term data from the AADC-011 study provided in clarification response A21, showing outcomes for participants in this study beyond the 12 months data presented in the CS, up to 60 months, demonstrates that of the [redacted] participants with follow-up data, [redacted] experienced an improvement in their motor milestone attainment at their longest follow-up timepoint compared to at 12 months. Additionally, [redacted] maintained their motor milestone achievement seen at 12-months at their longest follow-up timepoint. So, applying the LOCF approach to estimating missing data for these participants would be a conservative approach (i.e. it estimates maintenance,

when [redacted] actually improved). However, it is not clear to the EAG whether the LOCF approach was used to estimate motor milestone achievement for the participants in study AADC-011 beyond 12 months. Clarification response B18 states the approach was used to estimate outcomes for participants with less than five years data; this may mean it was used for the participants in AADC-011, but this is not clear. It is also unclear if the additional long-term follow-up data from study AADC-011 beyond 12 months was incorporated into the model.

Uncertainties we have identified around using the LOCF method are:

- If there is a possibility that any of the studies' participants with missing data experienced a decline in their motor milestone achievement at any point. While the consensus guidelines say that people do not generally show a deterioration in their symptoms over time, they state that if patients do show a decline in motor function this can be due to secondary factors.[5] This raises the possibility that a decline could happen, even if it is not due to the effect of the treatment waning. We also note that published data from the eladocagene exuparvovec studies shows that two participants (with data) experienced a decline in their motor scores three- and five-years post-surgery, respectively, associated with non-gene therapy related events.[1] This, again, shows a decline is possible.
- It is unclear from the CS and the company's clarification response how much missing data were estimated using the LOCF approach to arrive at the efficacy results used in the company's economic model scenario analysis (i.e. the results in CS Table 30). If a large amount of data were estimated using this approach, this may not be reasonable.

Due to these uncertainties, we also provide scenario analyses using the observed trial motor milestone achievement data with missing data not imputed.

The EAG notes that only 28 of the 30 participants enrolled in the eladocagene exuparvovec studies are included in the pooled analysis in the CS Table 30 rather than all 30 participants. The EAG suggests that this is due to two participants in study AADC-011 being lost to follow-up as they could not attend the 12-month visit. However, the reason for why only 28 participants are included is not explained in the CS. It is unclear to the EAG why the other two participants could not be additionally included in the pooled estimate, with their missing data estimated through the LOCF approach (i.e. carrying their motor milestone values from baseline forwards). This would be a conservative analysis.

EAG comment on pairwise meta-analysis

The EAG cannot check the company's pooled proportions of participants achieving motor milestones, as presented in CS Table 30. These data are used in a scenario analysis in the company's economic model. The EAG has opted to use these pooled proportions in our base case. We agree that the use of the LOCF approach appears reasonable for estimating missing data in the context of AADC deficiency treatment with eladocagene exuparvovec, but note uncertainties related to the implicit assumption that that people do not decline and a lack of clarity about how much data were missing and imputed.

3.3 Critique of studies included in the indirect treatment comparison (ITC) feasibility assessment and "naïve analysis" of best supportive care

3.3.1 Rationale for ITC

As outlined in section 2.3, the relevant comparator in the decision problem was defined as best supportive care. The eladocagene exuparvovec evidence base consisted of three single arm studies in this ultra-rare indication which were pooled together (N=28 participants, combined) (see section 3.2.6). The company explored the feasibility of conducting an ITC to compare the effectiveness of eladocagene exuparvovec to best supportive care. The rationale for this was that only single arm clinical trial data were available to assess the efficacy of eladocagene exuparvovec (i.e. that there were no comparative studies). The EAG agrees with the company's rationale.

3.3.2 Identification, selection and feasibility assessment of studies for ITC

3.3.2.1 Natural history database (NHDB): systematic literature review methods

To assess the effectiveness of best supportive care, the company compiled a natural history database (NHDB) of people with AADC deficiency. Unique cases were identified from published reports found through a systematic literature review (CS section B.2.9.1.3). The methods of the review are reported in a poster authored by Bergkvist et al (2021),[23] which the company provided with their submission. The poster is currently being written up as a manuscript for publication in a journal and was not available to share with NICE and the EAG (clarification response A32). Searches for the review were conducted up to 20th December 2019.[23] A further 13 references were considered for inclusion (clarification response A27), which were found through the company's separate CS systematic literature review conducted for this NICE appraisal. The searches for the latter review were conducted

on 23 February 2022 (clarification response A3), and so are up to date. The CS systematic review searches were more restricted than those of Bergkvist et al. (2021).[23] We believe that the CS searches may not have identified case reports. Therefore, the NHDB may not capture all recently published evidence. The company stated none of the 13 publications identified in the CS review were relevant (CS section B.2.9.2).

Publications were included in the Bergkvist et al (2021)).[23] review if they were case and case series reports, clinical studies of people with AADC deficiency, literature reviews, or conference presentations and abstracts (CS appendix D.1.1.8 and Bergkvist et al (2021)).[23] Publications that did not report patient-level clinical characteristics were excluded (CS section D.1.1.8). No other eligibility criteria appear to have been used. A total of 98 publications were included in the NHDB (CS appendix D.1.1.8)

3.3.2.2 Overview of participants included in the NHDB, ITC feasibility assessment and best supportive care naïve analysis

A total of 49 unique participants who had a severe phenotype of AADC deficiency were included in the NHDB. They were selected from an initial sample of 237 likely unique participants identified from the publications included in the NHDB. This was further reduced to a sample of 185 participants who were clearly unique participants or identified as being so through deduction (clarification response A36). From among these, 22 were identified as participants who had taken part in the eladocagene exuparvovec studies (clarification response A36; 22 participants calculated by EAG, rather than being explicitly stated in clarification response), leaving 163 participants who had not taken part in the eladocagene exuparvovec studies. Of the 185 unique participants, disease severity could be determined for 96 individuals. Of these, 69 were classified as having the severe phenotype (clarification response A25). The company defined the severe phenotype as “AADC deficiency with no or poor head control at 24 months” (CS section B.2.9.1.3), which the EAG considers appropriate, based on clinical expert advice to the EAG (see section 2.2.1). Of 69 with the severe phenotype, clarification response A25 states it was determined that 20 participants had taken part in the eladocagene exuparvovec studies. These participants were removed, leaving a final sample size of 49 participants for the NHDB.

The company then assessed the feasibility of conducting an ITC using the individual patient data (IPD) from the NHDB for best supportive care (n = 49 participants) and IPD from the eladocagene exuparvovec trials (N = 28 participants). The company chose a propensity score matching methodology (we critique this approach in section 3.4.2). This approach

matches participants treated with eladocagene exuparvovec to similar participants receiving best supportive care, based on their baseline characteristics (CS appendix D.1.1.8).

The company concluded that the ITC was not feasible (CS section B.2.9.7). Instead, the company carried out a "naïve analysis" of the 49 participants included in the NHDB (CS section B.2.9.6) to estimate the proportion of participants who achieved the motor milestones of full head alignment, sitting unassisted, standing with support (stepping) and walking with assistance over five years follow-up while receiving best supportive care (CS Table 29, CS section B.2.9.6 and CS Table 42, CS section B.3.3.1.2), as well as no motor milestone achievement. The proportions derived from this analysis for the achievement of motor milestones between baseline and year 5+ are used in the company's economic model base case (CS section B.3.3.1.2).

3.3.2.3 EAG critique of the identification and selection of evidence for the NHDB

The EAG considers that the searches for the Bergkvist et al. (2021)[23] systematic literature review were appropriate and up to date. The search strategy was broad, using only AADC terms. This would likely identify any references referring to this population. A range of appropriate sources were searched (Excerpta Medica database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE), BIOSIS Previews, AADC Research Trust website, and reference lists of review articles). The EAG believes that the review eligibility criteria were appropriate for identifying references that potentially reported on individual people with AADC deficiency (CS appendix D.1.1.8). The company's approach to deducing that people with AADC deficiency reported on in the literature were unique cases, as outlined in CS appendix D.1.1.8, also seems appropriate (and so we have not outlined it here). The company's clarification responses A25 and A36 provide sufficient information to make it relatively transparent how the 49 individuals for inclusion in the NHDB were identified. The EAG has no specific concerns about the process used.

The EAG, however, has the following concerns about the selection and identification of evidence for inclusion in the NHDB:

- The CS systematic review searches were more restricted than those of Bergkvist et al. (2021).[23] We believe that the CS searches may not have identified case reports. Therefore, the NHDB may not capture recently published evidence. It is uncertain whether or not this would affect the best supportive care naïve analysis results.
- Two independent reviewers screened results from the database searches for inclusion in the NHDB, with adjudication where needed by a third reviewer (CS

appendix D.1.1.8). This approach was appropriate. There is, however, a lack of clarity in the CS and in Bergkvist et al. (2021)[23] about whether two independent reviewers screened publications at the full text screening stage. If this approach was not used, there is a risk of bias in the selection of the evidence to include in the NHDB.

- None of the 13 publications identified as part of the CS systematic literature review were included in the NHDB (CS section B.2.9.2). We consider that there was a lack of clarity in CS Table 26 about why five of these were considered not to have sufficient data for inclusion (Pearson et al., 2020;[24] Saberian et al., 2021;[25] Saberian et al. (2021);[26] Williams et al. (2021);[27] and Wen et al. (2020)[28]). NICE and the EAG asked the company to further clarify why these studies were excluded (clarification question A37). It remains unclear to the EAG why the data included in (Pearson et al., 2020)[24] and Williams et al. (2021)[27] was considered insufficient for use in the NHDB. The company clarified that these studies were excluded as data were collected via questionnaires, including the use of online questionnaires with data combined with answers from parents and caregivers in the case of Pearson et al. 2020 (clarification response A37). Given that we understand from clarification response A39, that motor function results from studies were entered into the database “as is” from studies and two independent clinical experts used these data to determine the motor milestone achievement results (i.e. those pooled in CS Table 29), it remainsunclear to the EAG why the data in these two studies could not be used for this purpose. This raises the possibility that not all relevant publications, and thus not all unique individuals with ADDC deficiency, were included in the NHDB.

In summary, the EAG considers it uncertain whether all relevant publications have been included in the NHDB. There is a potential risk that not all relevant cases of AADC deficiency reported in the literature have been included in the NHDB. In turn, it is possible that the naïve analysis of best supportive care used in the company’s economic model is missing eligible cases.

3.3.3 Clinical heterogeneity assessment

To assess clinical heterogeneity, it is important to consider if there were any baseline characteristic differences between participants included in the eladocagene exuparvovec trials and those included in the best supportive care analyses derived from the NHDB. Baseline differences between treatments in terms of effect modifiers could bias the indirect comparison unless the analysis adjusts for these.[29] This is also salient as the naïve analysis

of best supportive care did not adjust for differences at baseline in prognostic factors, meaning it could be subject to bias.

CS appendix D1.1.8 states that, in the NHDB, demographic data collected about the participants included sex, age of diagnosis, mutation status, AIMS and PDMS-2 scores, country of treatment, ethnicity, and race. Yet in CS Table 27, the company compares the baseline characteristics of the participants in the NHDB against those of the participants in the eladocagene exuparvovec trials only in terms of sex, race, age at diagnosis and gene mutations (CS section B.2.9.3). We note these are the covariates participants were matched on in the ITC feasibility assessment (CS section B.2.9.4.1). We asked the company to extend CS Table 27 to include other baseline characteristics collected in the NHDB (clarification question A23), to allow a more comprehensive assessment of any baseline differences impacting the ITC or naïve analysis results.

As acknowledged in CS section B.2.9.3, it is difficult to compare how similar the baseline characteristics between the participants in the NHDB and the eladocagene exuparvovec studies were, due to lack of information about sex, race, and gene mutations for significant proportions of the individuals included in the NHDB (12.2%, 20.4% and 26.5%, respectively). The EAG notes that there were proportionally more female participants in the eladocagene studies (50.0%) than the NHDB (34.6%). There were also proportionally more participants of a White race in the NHDB (16.3%) than in the eladocagene studies (3.6%). Age at diagnosis was the same.

In response to clarification question A23, the only additional baseline information the company provided was baseline AIMS scores and disease severity (the company explained why other information could not be provided in clarification response A23). It is not possible to compare baseline AIMS scores between participants in the NHDB and the eladocagene exuparvovec studies, due to a large amount of missing data for participants in the NHDB. Disease severity (the severe phenotype) was defined essentially the same in the NHDB and eladocagene exuparvovec studies.

The CS does not discuss the factors that are prognostic of motor function development in AADC deficiency treatment of the factors that are treatment effect modifiers. We asked the company to summarise the evidence on the factors that are prognostic (clarification question A22). The CS states that sex, race, mutation category and age at diagnosis were selected as covariates to use in the ITC feasibility assessment “based on discussions with clinicians” (CS section B.2.9.4.1). The CS does not, though, provide the exact rationale for the

selection of these (for example, it does not state whether these factors were selected because clinicians considered them to be prognostic). The company provided the rationale for using the covariates that they selected in clarification response A22. The EAG believes the company's rationale is reasonable. The company notes in the response that baseline motor milestone achievement is considered a prognostic factor, and that the participants in the NHDB and eladocagene exuparvovec studies were already matched for this through having no motor function at baseline.

Overall we cannot conclude whether or not the NHDB participants were sufficiently comparable to those included in the eladocagene exuparvovec studies due to a lack of information. We do note a difference in sex, though, but it is unclear if this might bias the naïve analysis efficacy estimate of best supportive care.

3.3.4 Similarity of treatment effects

The CS provides limited information about how the motor milestone achievement outcomes from the NHDB were assessed and derived from the publications reporting individual cases. The only information available is in CS sections B.2.9.1.3 and B.2.9.4.2. Section B.2.9.4.2 suggests participants' achievement of motor milestones from year 1 to year 5 were assessed. No information is provided, however, about how the motor milestones were defined in the NHDB; the CS just repeats how they were defined in the eladocagene exuparvovec studies. CS section B.2.9.1.3 suggests that motor milestones in the NHDB were estimated using both quantitative (for example PDMS-2 and AIMS scores) and qualitative data reported in the publications. However, it is unclear from both this description and the Bergkvist et al. (2021)[23] poster if this information was just used to determine participants' disease phenotype (clarification question A38) or whether this is how the motor milestones achieved over time were assessed for the best supportive care efficacy estimate.

We asked the company to clarify if the definition of the motor milestones was consistent across the eladocagene exuparvovec studies and the NHDB (clarification question A26). In clarification response A26, the company states the definitions were "broadly consistent". Clarification response A39 states motor function information were extracted from publications into the NHDB and then two clinical experts (independent of the data extraction team) assessed motor milestone achievement from this information. Clarification response A26 states that the assessment of the motor milestones was anchored to those measured in the PDMS-2. The EAG notes that the terms full head control, sitting, stepping and walking used in the NHDB corresponded to the PDMS-2 items used for assessing full head control

(item #10), sitting unassisted (item #14), standing with support (item #28) and walking with assistance (item #34) in the eladocagene exuparvovec studies. It appears that the motor milestones were defined and assessed in a comparable way in the NHDB and eladocagene exuparvovec studies. The only concern the EAG has about how the motor milestone results were derived in the NHDB, is that it is unclear how objective and consistent the judgements made by the clinicians were. Two clinicians determined the motor milestones participants had achieved from the data extracted into the database. It is unclear, however, if each of these clinicians reviewed all data independently of each other and resolved any disagreements (thus improving the objectivity and consistency of the process), or if each reviewed only a subset of the data once and thus the motor milestones achievement status was determined by one clinician only in each case (which may result in less objectivity and may mean that data were not judged in a consistent way).

3.3.5 Details of best supportive care provided to participants in the NHDB

Bergkvist et al. (2021)[23] provides details of the best supportive care received by 135 people included in the database, but not specifically for the 49 people with the severe phenotype who were analysed in the CS. The company provided information on the care received by these 49 participants in the NHDB in clarification response A42. The company stated the treatment received was broadly reflective of that received in clinical practice in England. Our expert also stated that the care patients received was a good representation of the best supportive care provided in practice in England.

3.3.6 Risk of bias assessment for studies included in the ITC

The CS does not state if a quality assessment of the studies contributing data on individual participants to the NHDB was carried out. We asked the company to clarify if the studies were critically appraised. In clarification response A35, the company stated that the NHDB data had undergone a quality assurance process, but as the publications contributing data were case reports, case series and review articles, and no clinical studies were identified, these were not quality assessed. The EAG considers this reasonable.

EAG comment on the studies included in the ITC

The EAG has identified the following uncertainties about the evidence included in the NHDB:

- There is a potential risk that not all relevant publications, and thus not all unique cases of people with AADC deficiency in the literature, have been included in the NHDB.

- Aside from comparability in terms of disease severity, it is unclear if the 49 participants included in the NHDB CS analyses were sufficiently comparable to those included in the eladocagene exuparvovec studies.
- It is unclear how objective and consistent the process of determining each participants' motor milestone achievement was.

3.4 Critique of the indirect treatment comparison (ITC)

The company explored the feasibility of conducting an ITC comparing eladocagene exuparvovec to best supportive care. As described in section 3.3, the evidence base for best supportive care was a "patient-level" natural history database (NHDB) compiled by the company from published studies for the purposes of supporting regulatory and reimbursement applications (CS section B.2.8.1.3). Best supportive care was not defined, but as stated in section 3.3.5, the company provided information in clarification response A42 about the care received by the 49 participants identified from the NHDB for the best supportive care efficacy estimate. Also as stated in section 3.3.5, clinical expert advice to the EAG was that the care provided to the participants was a good representation of the care provided in clinical practice in England.

The methodology proposed for the ITC was propensity score matching (PSM) (CS section B.2.9.3), which requires individual participant data (IPD) for both eladocagene exuparvovec and best supportive care (TSD17).[30] PSM requires matching on all known prognostic factors across studies.

The only outcome included in the ITC was motor milestones achieved, a categorical variable (this was the sole eladocagene exuparvovec trial outcome used in the economic model, except for adverse events) which was derived from the PDMS-2 (see section 3.2.3).

The Company concluded that PSM methodology was inappropriate given substantive reductions in the best supportive care arm effective sample size (ESS) after matching and reverted to a naïve indirect comparison, which, by definition, did not adjust for any imbalance in prognostic factors across studies.

3.4.1 Data inputs to the ITC

The ITC analysis compared the pooled eladocagene exuparvovec data (n = 28) with the company's NHDB dataset for best supportive care (n = 49). Data on sex, age at diagnosis, race, gene mutations, PDMS-2 at baseline, AIMS at baseline, disease severity, motor

milestone achievement, mortality, and treatment were collected in the NHDB (CS sections B.2.9.1.3 and D.1.1.8).

The company consulted clinical experts about the factors that are prognostic of motor function development in AADC deficiency. The experts noted a lack of evidence on prognostic factors in AADC deficiency (clarification response A22). Nonetheless, the experts identified a number of prognostic factors, although their answers were variable. Many were unavailable in the publications included in the NHDB (clarification response A22). Ultimately, therefore, it was only possible to include sex, race, and mutation category as matching variables.

Sets of variables included in the analysis were (i) sex, race, mutation status, and age at diagnosis, (ii) sex, and race, (iii) sex. A subsequent analysis including mutation status alone was reported in clarification response A29.

3.4.2 Statistical methods for the ITC

As noted above the company favoured PSM to compare eladocagene exuparvovec to best supportive care, adjusting for imbalances in reported prognostic factors. This methodology requires IPD for treatment and control studies. The Company favoured this methodology over aggregate population matching methods since they were able to construct an IPD database (the NHDB). Furthermore, it appears unlikely that a suitable aggregate data source with sufficient subjects exists for best supportive care to facilitate a matching-adjusted indirect comparison (clarification response A27).

The PSM analysis was conducted in *R* using the *MatchIt* package. The code was provided and looks to have been correctly implemented. However, no data were provided to validate the analysis (clarification response A33).

Motor milestone results for the propensity score matching exercise were reported following in clarification response A29 (the results were not provided in the CS). Best practice is to use more than one method (TSD17)[30] but only logistic regression was considered.

PSM resulted in a low ESS when matching by sex, race, mutation category and age at diagnosis (effective sample size (ESS) = 1.16), or sex and race (effective sample size = 8.08) (CS Table 28). Distribution of patient weights after matching show a large proportion of participants given a zero weight and few participants receive very high weights (CS Figure

39). The analysis including sex alone yields a higher ESS (29.81) but was rejected by the company because of the weights distribution. The company clarified this was because "a small number of patients therefore carry an excessively large weight" (clarification response A28). However, the EAG disagrees with this assessment as a sizable proportion of patients are given higher weights and the weights at around 1.8 are not excessive (Figure 2, clarification response A28). Nevertheless, given the lack of reporting of prognostic factors, the EAG considers a reasonable range of sensitivity analyses (i.e. the results provided for different sets of matching covariates in the clarification response A29, Table 9) have been conducted for the PSM analysis.

A naïve indirect comparison was thus preferred by the company. All 28 eladocagene exuparvovec participants and 49 NHDB participants were included. Only 2 out of the best supportive care participants experienced improvement in motor milestones over five years compared to substantive improvements with eladocagene exuparvovec (see section 3.5). The naïve analysis, whilst being imperfect in not adjusting for observed (and unobserved) prognostic factors, is more conservative (i.e. favours best supportive care) than each of the adjusted analyses (in which fewer BSC participants achieve motor milestones) (clarification response A29). The EAG therefore agrees with the use of the naïve analysis. However, concerns remain with respect to:

- Potential differences in unobserved prognostic factors between the studies.
- How objective and consistent the process of retrospectively anchoring the motor function data to the motor milestone achievement states measured by the PDMS-2 was (see section 3.3.4).

3.4.3 Summary of EAG critique of the ITC feasibility assessment and "naïve analysis" of best supportive care

- The NHDB for this submission was not updated using the same methodology as the original work, particularly with respect to study design; recent data relating to people with AADC deficiency could therefore have been missed.
- The NHDB data were not provided for the EAG to validate.
- The ITC methodology followed by the company is appropriate given the available data.
- The methodology has been described and applied correctly.
- Observed prognostic factors have been included in the PSM analysis.
- There may be differences in unobserved prognostic factors not adjusted for in the analysis.

- A range of scenario analyses for the PSM were conducted.
- The PSM analyses could not be validated as IPD were not provided.
- The unadjusted "naïve" ITC results do not adjust for imbalances in prognostic factors across studies hence their interpretation is subject to bias. However, the naïve analysis is more conservative (favours best supportive care) than the adjusted analyses.

3.5 Results from the indirect comparison

CS section B.2.9.6 reports the results of a naïve analysis, with CS Table 29 providing the distribution of patients across motor milestone health states in the best supportive care arm (derived from the NHDB). As stated in section 3.2.6, Table 30 shows the observed distribution of patients across motor milestone health states in the eladocagene exuparvovec arm (with the LOCF approach applied to estimate missing data) (Table 22). We critique the eladocagene exuparvovec pooled analysis in section 3.2.6. Here we focus on the best supportive care efficacy estimate derived from the NHDB. We provide the pooled eladocagene studies' results here for comparison, however.

Clarification response A45 confirmed that the motor milestone results in CS Tables 29 and 30 show the proportion of patients who were classed as showing 'newly emerging' abilities or 'mastery'.

Clarification response A46 provided an updated version of CS Table 29 with the numbers of patients, in addition to the percentages that were originally reported, of patients distributed across motor milestone health states in the best supportive care arm. The EAG were therefore able to verify that the percentages in CS Table 29 are correct (that is, all 49 participants included in the NHDB were also included in the analysis).

Table 21: Distribution of patients across motor milestone health states in the best supportive care arm (derived from the NHDB)

	No motor milestone N (%)	Full head alignment N (%)	Sitting N (%)	Stepping N (%)	Walking with assistance N (%)
Baseline	49 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Year 1	48 (98%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Year 2	47 (96%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Year 3	47 (96%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Year 4	47 (96%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)

	No motor milestone N (%)	Full head alignment N (%)	Sitting N (%)	Stepping N (%)	Walking with assistance N (%)
Year 5 +	47 (96%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)

Abbreviations: BSC – best supportive care; NHDB – natural history database
**Baseline is 24 months of age, in line with the age criteria used to define the N=49 NHDB population*
Reproduction of company clarification A46 Table 13

The EAG clinical expert confirmed that the percentages of patients achieving each motor milestone in Table 21 are similar to the percentages of patients achieving the same motor milestones when receiving best supportive care in their clinical experience.

Table 22: Observed distribution of patients across motor milestone health states in the eladocagene exuparvovec arm

	No motor milestone	Full head alignment	Sitting	Stepping	Walking with assistance
Baseline	100%	0%	0%	0%	0%
Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The highest motor milestone achieved at that timepoint is reported. N=28
Reproduction of CS Table 30

With the caveat that the EAG cannot verify the data in CS Table 30 and the uncertainty around the use of LOCF, the EAG agree with the company's finding that the naïve analysis suggest that severe AADC deficiency patients receiving best supportive care show minimal or no improvement in terms of their motor milestone, while patients receiving eladocagene show improvements in patients' motor milestones over a similar time period.

3.6 Additional work on clinical effectiveness undertaken by the EAG

None.

3.7 Conclusions on the clinical effectiveness evidence

The company's decision problem addressed the NICE scope. The company included three single-arm studies of eladocagene exuparvovec in the CS (AADC-010, AADC-011 and AADC-CU/1601). The included studies adequately reflect the company's decision problem, the NICE scope and the [redacted]. However, the studies were single arm and did not include a comparator. The company addresses the comparator

element of the NICE scope and their decision problem through their “naïve analysis” of the efficacy of best supportive care, using individual participant data from the literature. The results of this analysis were used in the company’s economic model base case. The eladocagene exuparvovec trial participants were generally representative of the people with AADC deficiency seen in clinical practice, except for race and, associated with this, genotype (all the participants had the founder mutation).

The eladocagene exuparvovec studies found improvements in motor milestone achievement, motor function and other AADC deficiency symptoms. There were reductions in the number of hours of oculogyric crisis patients experienced. Many aspects of caregiver quality of life improved. The most common adverse events were pyrexia and dyskinesia.

The EAG’s risk of bias assessment of the eladocagene exuparvovec trials identified some concerns about risk of bias from the single arm design of the trials, but we generally considered the trials to be of a good quality. The EAG has, however, identified the following uncertainties associated with the eladocagene exuparvovec and best supportive care efficacy evidence presented in the CS:

- The EAG identified three ongoing studies, conducted in Japan, with data published for participants with the severe phenotype who received AAV-hAADC-2 administered into the putamen.[11] It is unclear if this AADC-expressing AAV vector is the same as the one used in the eladocagene exuparvovec studies and therefore whether these data are relevant to this appraisal.
- All participants in the trials had the founder mutation. It is unknown if genotype might impact on clinical effectiveness of eladocagene exuparvovec, as no evidence is available, but theoretically it may not. Nonetheless, clinical expert advice to the EAG is that ideally the gene therapy should be tested on a broad spectrum of AADC genotypes.
- A strength of the studies is the collection of long-term data beyond the original trial periods. However, these long-term data are not available for all enrolled participants. The outcomes for those not followed up in the long-term are unknown. An uncertainty is whether or not the participants who were not followed up differed to those who were in a way that may bias the results. Therefore, the longer-term impact of eladocagene exuparvovec on motor milestone achievement (and other outcomes) is subject to uncertainty.
- Only a narrative summary of the long-term data beyond 12 months in study AADC-011 and five years in studies AADC-010 and AADC-CU/1601 was provided. This

makes it difficult to determine the exact numbers and proportions of participants who had achieved motor milestones at each follow-up timepoint and whether there were any fluctuations in the trajectory of participants' achievement of these milestones over time.

- The EAG believes that the company's use of the LOCF approach to estimating missing data in the pooled motor milestone analysis presented in Table 30 is acceptable. We note, however, that it is theoretically possible that rather than maintaining their last highest motor milestone achieved (as the LOCF approach assumes), that some participants with missing data might have experienced a decline in their motor function. If any had, this would make this imputation approach inappropriate. Additionally, the extent of missing data imputed is unclear, so it is difficult to fully determine if the use of the LOCF approach was reasonable.
- It is not clear why data from 28 of the 30 enrolled participants are used in the pooled analysis of the three eladocagene exuparvovec studies rather than all 30 participants, in CS Table 30 (i.e. the data that informs the company's scenario analysis). The EAG assumes that this is due to two participants in study AADC-011 being lost to follow-up due to not being able to attend the 12-month visit. It is unclear to the EAG why these participants could not be additionally included in the pooled estimate, with their missing data estimated through the LOCF approach (i.e. carrying their motor milestone values from baseline forwards), which would be a more conservative analysis.
- There is a lack of clarity in the CS about whether or not any participants experienced a decline in their motor function after receiving eladocagene exuparvovec. From the long-term data reported in clarification response A21 and findings reported in Tai et al. (2022),[1] there appear to have been three instances of motor function declining at some point during the trials due to secondary factors. It is unclear if any other participants experienced a decline.
- It is unclear if the long-term follow-up motor milestones achievement results collected between >12 months and five years post-surgery in study AADC-011 have been used in the company's economic model scenario analysis, which uses the motor milestone achievement results directly from the studies.
- There are a couple of methodological uncertainties related to how the naïve, unadjusted motor milestone achievement efficacy estimates for best supportive care were obtained. It is uncertain whether or not all relevant AADC deficiency cases from the literature were identified and included in the analysis. It is unclear how objective and consistent judgements made about participants' motor milestone achievement

results were across the database. Additionally, as the naïve analysis does not adjust for imbalances in prognostic factors (i.e. between people who received eladocagene exuparvovec and those receiving best supportive), the results may be subject to bias due to potentially unaccounted for differences between participants which may impact on their motor milestone achievement. Despite these concerns, based on clinical expert opinion, the EAG suggests the efficacy estimate derived for best supportive care is a reasonable representation of the efficacy of best supportive care in clinical practice.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature search to identify published cost-effectiveness studies for AADC deficiency. The search, reported in CS Appendix G, was conducted in February 2022. Results are presented in CS Section B.3.1.

Only one study was included, a conference abstract summarised in CS Table 114 Appendix G.[31] Briefly, the abstract reports a UK based modelling study sponsored by the company. The study was conducted from the NHS perspective and assessed the long-term benefit of gene-replacement therapy in people with AADC deficiency compared to best supportive care. The model consists of two phases: the development phase for the first years after treatment and a long-term phase for patients beyond that. The company stated that this study was used as the basis of the cost-effectiveness analysis in the current appraisal. In terms of results, the abstract reported a total of 17.30 undiscounted QALYs over a lifetime horizon. However, results in terms of treatment efficacy or costs were not reported.

EAG conclusions: The reporting of the search strategies and results of the company's systematic literature review was clear. The searches conducted were up to date and included good database coverage and wide range of grey literature. The EAG believe the company's review would identify all relevant economic evaluation on AADC deficiency.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The EAG assessed the company's economic evaluation against NICE Reference Case requirements, as shown in Table 23.

Table 23 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes (See Section 4.2.5)
Perspective on costs	NHS and PSS	Yes (See Section 4.2.5)
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes (See Section 4.2.2)
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. The base case model has a lifetime horizon (See Section 4.2.5)
Synthesis of evidence on health effects	Based on systematic review	Yes (See Section 4.2.6)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. The model estimates QALYs. Health state utilities are obtained using time-trade off (TTO) methodology (See Section 4.2.7)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes (See Section 4.2.7)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. TTO estimates were obtained from UK general population (See Section 4.2.7)
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes. Due to the severity of the condition in patients with AADC deficiency, the company estimated a QALY weight (modifier factor) based on the undiscounted incremental QALY gain per patient over lifetime horizon from eladocagene exuparvovec versus best supportive care (See Section 5.1)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes (See Section 4.2.8)
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	A discount rate of 1.5% was applied for both costs and health effects in the base case. We

		disagree with the company's approach. (See Section 4.2.5)

4.2.2 Model structure

The model structure is informed by the modelling approach adopted in a previous NICE HST on the treatment of spinal muscular atrophy (SMA) (NICE HST 15) (CS Section B.3.2.2.2).[32] They developed a cohort model with six health states, five of which are based on the motor milestones observed in the three pivotal clinical trials. These are (from 'worst' to 'best'): 'no motor function', 'full-head control', 'sitting unassisted', 'standing with support', and 'walking with assistance'. The final state, death, is an absorbing state. A schema of the company's model is reproduced from CS Figure 40 in Figure 1 below.

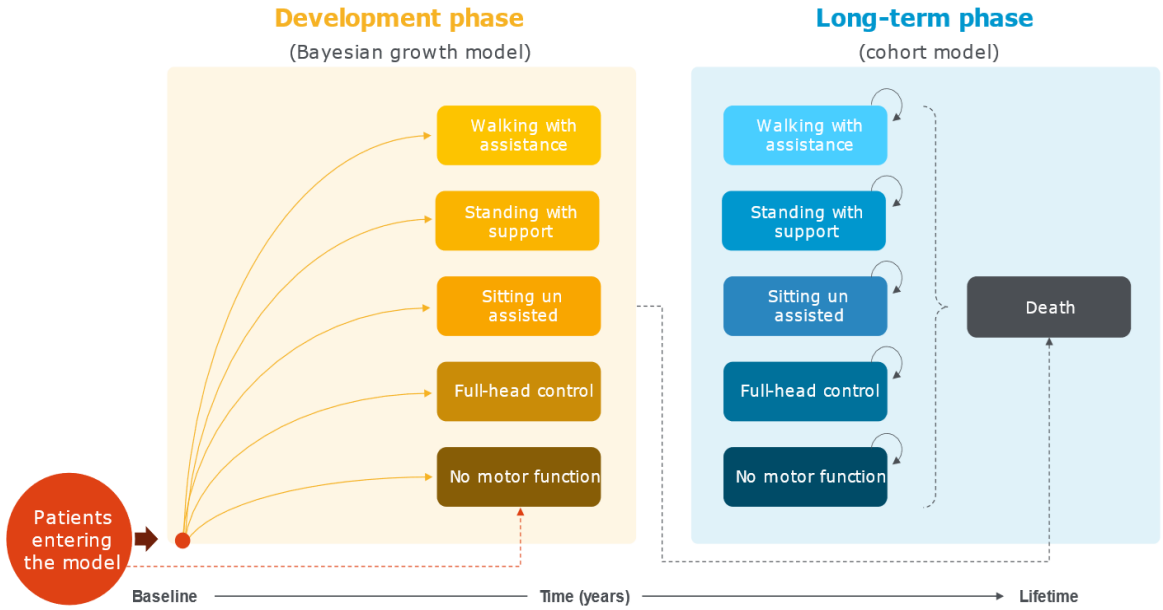


Figure 1 Company's model structure

Source: reproduced from CS Figure 40

The model includes two phases: a short-term development phase (for the initial 12 years) and a long-term phase (beyond 12 years up to lifetime).

Short-term development phase (for the initial 12 years)

In the eladocagene exuparvovec arm, observed individual patient-level (N=28) total raw PDMS-2 scores were used from the three clinical trials (AADC-010, AADC-011, and AADC-CU/1601) to inform a Bayesian growth curve model to estimate patient distribution in the health states. This approach included:

- fitting a parametric curve (Gompertz for the company's base case) to the observed PDMS-2 data from the clinical trials in the Bayesian model to predict PDMS-2 scores up to 12 years post-gene replacement.
- using the above predicted PDMS-2 scores as the only covariate in a cumulative ordered logit model to predict the motor milestone achievement.

The company justified the use of growth models to account for heterogeneity between participants in achieving motor milestones and in plateauing in motor development (that is, patients were not expected to progress further to higher motor milestone states). For further details, see CS Section 3.3.1.1.2 and the company's response to clarification question B1. It is stated that a Bayesian approach was adopted to address a small sample size (N=28), missing data, and limited follow-up. A detailed critique of the company's approach is in Section 4.2.6 of this report.

The company argue that improvements in cognitive function and other AADC deficiency related symptoms (e.g., cognition, behaviour, movement, and oculogyric crises) are implicitly captured within the improvement in motor milestones. This assumption is not incorporated in the Bayesian growth model but is implicitly incorporated in the model through the estimation of health state utilities, which we discuss later in Section 4.2.7 of this report.

For the best supportive care arm, the company used the natural history database (NHDB) (discussed earlier in Section **Error! Reference source not found.**) to estimate the distribution of patients across the health states.[23] We discuss this in Section 4.2.6.1.2**Error! Reference source not found.**.

Long term phase (beyond 12 years up to lifetime):
In this phase, patient distribution between health states is driven by mortality. Patients are assumed to remain in a static motor milestone state achieved during the developmental phase until death. They are attributed a probability of death in each of these motor milestone health states, which was estimated using survival curves from a study on patients with a proxy condition – cerebral palsy.[33] We critique the company's approach of survival estimation in Section 4.2.6 of this report.

The model cycle length is 3 months. This is reflective of the assessment timepoints in the clinical trial AADC-011. We agree with the company and consider this time length to sufficiently capture the clinical outcomes in patients with AADC-deficiency. A half-cycle

correction was appropriately applied in the model. A detailed critique of the company's approach to modelling efficacy parameters, including motor milestone achievement and survival, is presented in Section 4.2.6; HRQoL in Section 4.2.7; and costs and resource use in Section 4.2.8**Error! Reference source not found.** of this report, respectively.

EAG conclusions:

- Based on our expert clinical advice, we view spinal muscular atrophy as an acceptable proxy condition to inform the model structure for AADC deficiency as it has similar motor symptoms. Cerebral palsy is another acceptable proxy condition to AADC deficiency, which the company used to inform survival estimates.
- We agree with the company's approach of including two phases in the model. The duration of the development phase is assumed to be 12 years in the base case, compared to five years of trial follow-up. We view this is a reasonable assumption based on clinical advice we received, as the development duration is consistent with that of development of a healthy child. Furthermore, varying the duration doesn't have any significant impact on the overall cost effectiveness results as a very small proportion of patients improve between 5 and 12 years in the economic model (see CS Tables 76 and 77).
- We agree with the company's approach to use motor milestone health states in their economic model because: i) the primary efficacy endpoint in the three pivotal trials was the achievement of key motor milestones (CS Section B.2.6); and ii) clinically, motor development delay is an important consequence of AADC deficiency.
- However, we have concerns about the company's preferred approach of using PDMS-2 scores to derive motor milestone health state. We discuss this in detail in Section 4.2.6.1 of this report.
- In the long-term (i.e., beyond 12 years of model entry), the company assumed no gain or loss of motor function (that is, no forward or backward transitions to better or worse motor milestone health states), once gained in the development phase. This is a reasonable simplifying assumption. We acknowledge that data from the clinical trials of eladocagene exuparvovec demonstrated patients generally maintained the highest motor milestone they achieved at their longest follow-up timepoint during the AADC-CU/1601 and AADC-010 trials longer-term follow-ups (see Section **Error! Reference source not found.**). There is no evidence of AADC deficiency being a neurodegenerative disease from the natural history studies. Also, our clinical expert indicated that they did not come across any patients showing a loss of skills or

regression. Nonetheless, there remains uncertainty over this assumption due to lack of available long-term data, particularly beyond 10 years.

4.2.3 Population

Baseline characteristics of the modelled cohort are based on participants in the three clinical trials for eladocagene exuparvovec: mean age 4 years; mean body weight 11.1 kg; severe phenotype with no motor function. See section 3.2.1.7 for a discussion of the characteristics of the trial populations. No subgroup analyses were conducted; this aligns with the NICE scope.

In the company's base case model, patients enter the short-term development phase at 4 years of age and the long-term phase at 16 years of age.

EAG conclusions: The modelled population is consistent with the licensed indication for eladocagene exuparvovec and the population specified in the NICE scope. Based on our clinical expert's advice the baseline characteristics are reflective of clinical practice, except the mean age of the modelled population is lower than expected in clinical practice. As will be presented in Section 6, we conduct three scenario analyses varying the mean age of the population finding that these influence the base case ICERs only slightly.

4.2.4 Interventions and comparators

The company model included the following:

- Intervention: Eladocagene exuparvovec + best supportive care
- Comparator: Best supportive care

The company described the intervention in their decision problem in CS section B.1.2; we discussed the intervention and its intended use in practice earlier in Section 2.2.2. The comparator arm, best supportive care, constitutes a combination of: i) a basket of symptomatic treatments (detailed in CS Section B.3.2.3.2), ii) multidisciplinary team support from specialists, including gastroenterologist, neurologist, pulmonologist, ear/nose/throat (ENT) doctor, ophthalmologist, endocrinologist, orthopaedic surgeon, geneticist, speech therapist, dietician, and occupational therapist , and iii) several medical and technical procedures (such as barium swallow test, blood test, coagulation test, MRI, ECG, X-ray etc..). We discuss these later in Section 4.2.8 of this report.

EAG conclusions:

- The modelled intervention and comparator are consistent with the NICE scope. We

view the comparator arm is reflective of the current established clinical management in England.

- We agree with the company's assumption that patients receiving eladocagene exuparvovec will also continue to receive best supportive care. This is reflective of our clinical expert's expectation of clinical practice if eladocagene exuparvovec is introduced.
- We note that participants in one of the three trials received one of two different doses of eladocagene exuparvovec. Nine of the 12 participants in AADC-011 received a higher dose of eladocagene exuparvovec (2.4x10vg doses) compared to that specified in the [redacted] (for further details, see section 3.2.1.3). In the economic model, the company used the pooled results from both the doses. Advice from our clinical expert indicated that the two separate doses are unlikely to have different efficacy. Therefore, we view the company's approach of pooling the results from both the doses to be appropriate.

4.2.5 Perspective, time horizon and discounting

The company appropriately uses a lifetime horizon to reflect the life-long condition of AADC deficiency. Their analyses take the perspective of the NHS and PSS in England, which aligns with the NICE manual for health technology evaluations. Costs and outcomes (life years and QALYs) are discounted at 1.5%. The company provide their rationale for applying this discount rate in CS Table 39.

EAG conclusions on discounting: The NICE manual for health technology assessment[34] suggests that a non-reference discount rate of 1.5% for both costs and effects may be considered if all of the following conditions are met: i) the technology is for people who would otherwise die or have a very severely impaired life; ii) it is likely to restore them to full or near-full health; and iii) the benefits are sustained over a very long period. While we view that eladocagene exuparvovec is targeted for patients with severely impaired life and who have missed key development steps by the time they are diagnosed and treated, it remains unclear: i) if the technology will restore patients to full or near-full health and ii) persistence of the benefits in the long term. Advice from our clinical expert suggests that eladocagene exuparvovec is unlikely to restore patients to full or near-full health as the gene-therapy is not curative. Secondly, while we acknowledge early indications of treatment benefits persisting based on the evidence of benefit up to 10 years in the study by Tai et al.[1] and data provided by the company in clarification response A21, there is currently no data to support persistence of treatment benefit in the long-term beyond 10 years. Considering the above

uncertainties, we view that a discount rate of 3.5% is appropriate for both costs and effects in the current appraisal.

We note that the discount rate has a significant impact on the overall cost-effectiveness results (see CS Tables 76 and 77). Therefore, we present the EAG scenarios using discount rates of 0%, 1.5% and 3.5% (shown in section 6).

4.2.6 Clinical parameters

The company used two sets of clinical parameters in their economic analysis:

- Development phase: Motor milestone achievement
- Long term phase: Survival using parametric distributions.

4.2.6.1 Motor milestone achievement

4.2.6.1.1 Eladocagene exuparvovec

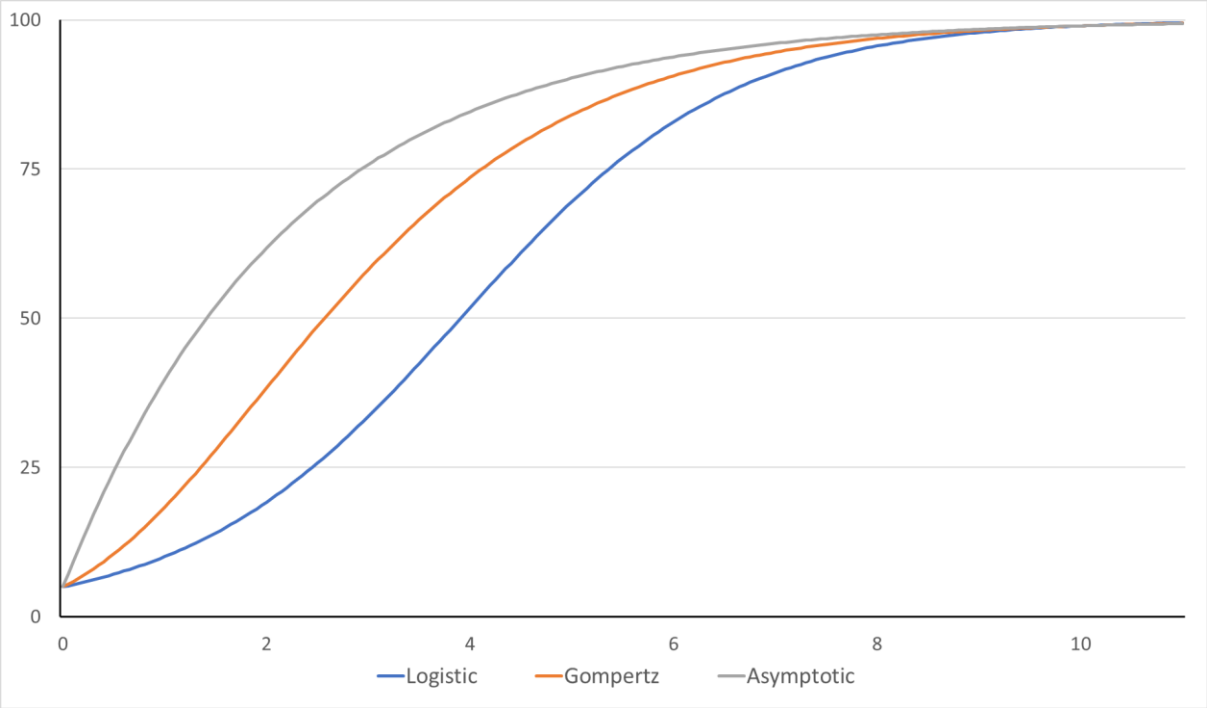
To inform the motor milestone health states, the company used PDMS-2 scores to predict motor milestone achievement; further details on the company's rationale are in CS Section B.3.2.2.7. We present a summary and critique of the company's approach below.

- ***Step 1: Bayesian modelling to predict PDMS-2 scores***

The company fitted a Bayesian growth curve model to the observed individual PDMS-2 scores and extrapolated them up to 12 years. They used a mixed-effects model due to heterogeneity across patients in improvements in PDMS-2 scores. Only raw PDMS-2 scores from the clinical trials were used to estimate motor milestone; other outcomes including age at baseline and Bayley-III scores were not used. Further details on company's rationale are in CS Section B.3.3.1 and Appendix J.

The company fitted Bayesian regression models (asymptotic, logistic and Gompertz) approaching an asymptote as patients' progression towards achieving developmental milestones was assumed to eventually plateau. An illustrative schematic of the three growth models is presented in
Figure 2 (reproduced from CS Appendix J Figure 62). The x-axis represents different time points in years (with 0 being when eladocagene exuparvovec was administered) and the Y-axis represents PDMS-2 scores. The curves represent change in PDMS-2 score over time. For example, the logistic model takes an 'S' shape indicating that the rate of change is slow at the beginning, then rising quickly before slowing down again and then reaching a plateau.

The Gompertz curve also takes an 'S' shape but it indicates a higher initial rate of increase in the score.



[redacted]

Figure 2 An illustrative schematic of the Bayesian growth models
Source: reproduced from CS Figure 62
Note: The x-axis represents different time points (duration in years) and the Y-axis represents PDMS-2 scores.

The company evaluated the goodness-of-fit of the three growth models in Figures 63 and 64 of CS Appendix J and Figure 4 of their response to EAG clarification question B4. The Gompertz distribution was used in their base case, which they stated, was based on goodness of fit and clinical validation. The asymptotic model was used in scenario analysis, which reduced the ICER for eladocagene exuparvovec vs best supportive care to [redacted] from the base case ICER of [redacted]. This is driven by a sharp increase in the rate of change in PDMS-2 scores before plateauing.

- ***Step 2: Cumulative ordered logit modelling to predict motor milestones***

The predicted PDMS-2 scores from Step 1 are used to predict motor milestone achievement in the economic model using a cumulative ordered logit model. The company explained their rationale for using this statistical model in their response to EAG clarification question B1(a). CS Table 41 presents the predicted distribution of patients across the motor milestone health states based on the cumulative ordered logit model.

In the cumulative ordered logit model, only PDMS-2 was used as a covariate. Other covariates including age at baseline and Bayley-III were excluded; the company reported that inclusion of these covariates either resulted in increased uncertainty in the model results or led to a smaller sample size informing the model.

The median estimate obtained by the company for the cumulative ordered logit models that used PDMS-2 scores as a covariate was [redacted] (95% Credible Interval: [redacted], [redacted]). The base case coefficient of 0.059 indicated greater motor milestone achievement with increment in PDMS-2 scores. The EAG conducted scenario analyses varying the PDMS-2 coefficient, for details see Section 6.

In Figure 3, we present a diagrammatic representation of the company's process of using PDMS-2 trial data to estimate motor milestone health states for the eladocagene exuparvovec arm.

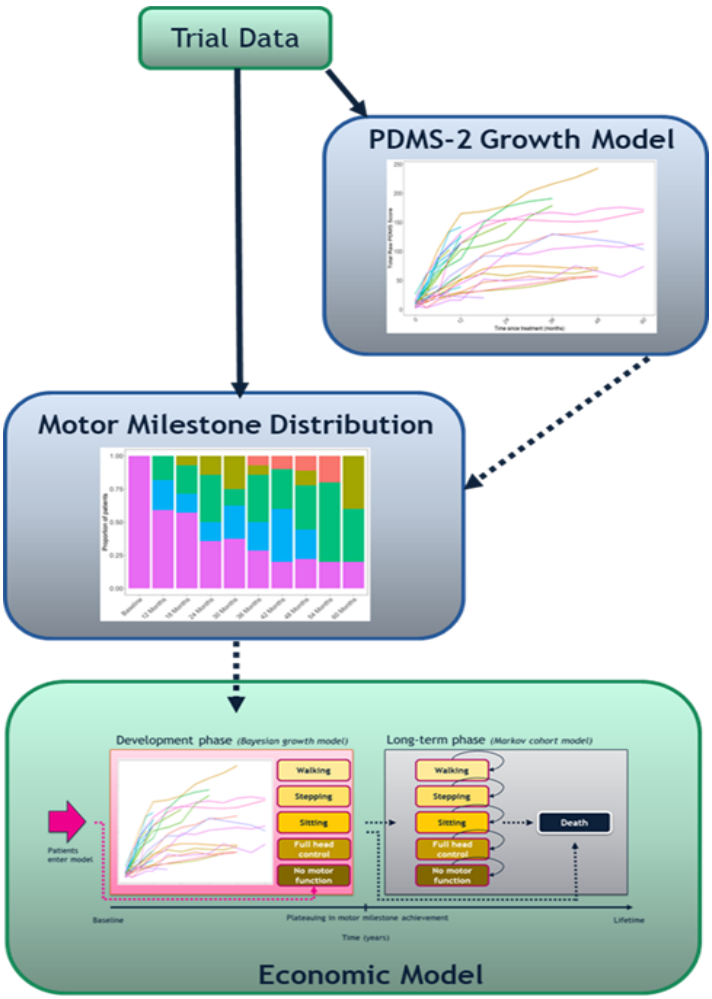


Figure 3 Diagrammatic presentation of the company's approach of using trial data for estimating motor milestone achievement for eladocagene exuparvovec in the model
Source: reproduced from CS Figure 41
Note: Solid arrows indicate estimation of models and dashed arrows represent where estimated fitted values from models are used.

The company conducted a scenario analysis using the observed distribution of patients across motor milestone achievement pooled from the three single arm eladocagene exuparvovec trials (CS Table 30). These estimates were obtained from a naïve analysis where missing data were imputed using the LOCF approach. We discuss and critique the company's naïve analysis earlier in Section 3.2.6 of this report. This scenario has a significant impact on the overall cost-effectiveness results, increasing the base case ICER for eladocagene exuparvovec versus best supportive care from [redacted] to [redacted].

EAG conclusions:
We believe the Bayesian growth curve model is a reasonable approach to the analysis, provided the asymptote assumption is appropriate. We agree with the company's rationale for using a mixed effects model and view their choice of the Gompertz model in their base case as reasonable. However, the growth model is reliant on the assumption that there is no deterioration of motor milestones. We are unable to ascertain the validity of this assumption as the company did not report the motor milestone trajectories of the 28 patients. Furthermore, we note that in CS Figure 58 of Appendix J there is at-least one patient with a downward PDMS-2 trajectory which contradicts the company's asymptote assumption.

However, the EAG have several concerns about the company's approach of using PDMS-2 scores to predict motor milestones:

- Consultation with our clinical expert suggested that assessment of motor milestones in a busy NHS clinic is not usually based on formal motor scales, except perhaps GMFCS grades/categories. We note the motor milestone achievement states seem to be more reflective of how motor function is assessed in practice than the PDMS-2 scores. For further details see Sections 3.2.3.1 of this report. Furthermore, [redacted] The primary outcomes of full head control, sitting unassisted, standing with support, and walking with assistance obtained from the clinical trials are important and clinically valid.

- Comparing the company's predicted distribution of patients across the motor milestone health states (based on PDMS-2 scores) with the observed distribution from the trials naïve analysis with LOCF, we observe that the predicted estimates in the 'worst' health state - 'no motor function' - is lower compared to the observed value (presented in
-
- Table 24 and Figure 4 below). Whereas for the remaining health states, the predicted estimates are, in general, higher than in the observed distribution. In particular, for the 'best' motor milestone state- 'walking with assistance' the predicted estimates are significantly higher than the observed distribution. This is an important issue as using the predicted motor milestone health states would potentially overestimate the effectiveness of eladocagene exuparvovec, favouring the intervention arm compared to best supportive care. For further discussion see Section 3.5 of this report.
- For the studies included in the NHDB for best supportive care, motor function results were mapped ('anchored') to how the motor milestone achievement results were classified in the eladocagene exuparvovec studies (i.e. anchored to the same measurement items from the PDMS-2). Using the observed patient distribution for eladocagene exuparvovec obtained from the naïve analysis is consistent with the approach adopted for the best supportive care (CS Table 29).

Considering the above uncertainties associated with using PDMS-2 scores as a predictor for motor milestone achievement, we view it as appropriate to use the observed patient distribution across the motor milestone health states from the three eladocagene exuparvovec studies as the base case for this appraisal. We use this assumption in EAG preferred assumptions (see Section 6.2). For completeness, we also conduct scenario analyses using the observed patient distributions based on i) the original sample, without missing data imputed by the LOCF approach and using the baseline number of participants included in the trials as the denominator; and ii) the distribution with the number of people followed up is used as the denominator, rather than the number of people at baseline per follow-up (see Section 6).

Table 24 Comparison of the predicted distribution of patients across motor milestones using Bayesian growth models in the company's base case with the observed estimates based on naïve analysis used in the company scenario analysis for Eladocagene Exuparvovec arm

	No motor milestone		Full head count		Sitting		Standing with support		Walking with assistance	
	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed

Baseline	[redacted]	100%	[redacted]	0%	[redacted]	0%	[redacted]	0%	[redacted]	0%
Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimates are rounded to nearest decimal; Observed values are based on naïve comparison that used last observation carried forward approach to impute missing data. Predicted values are extracted by the EAG from the company's model										

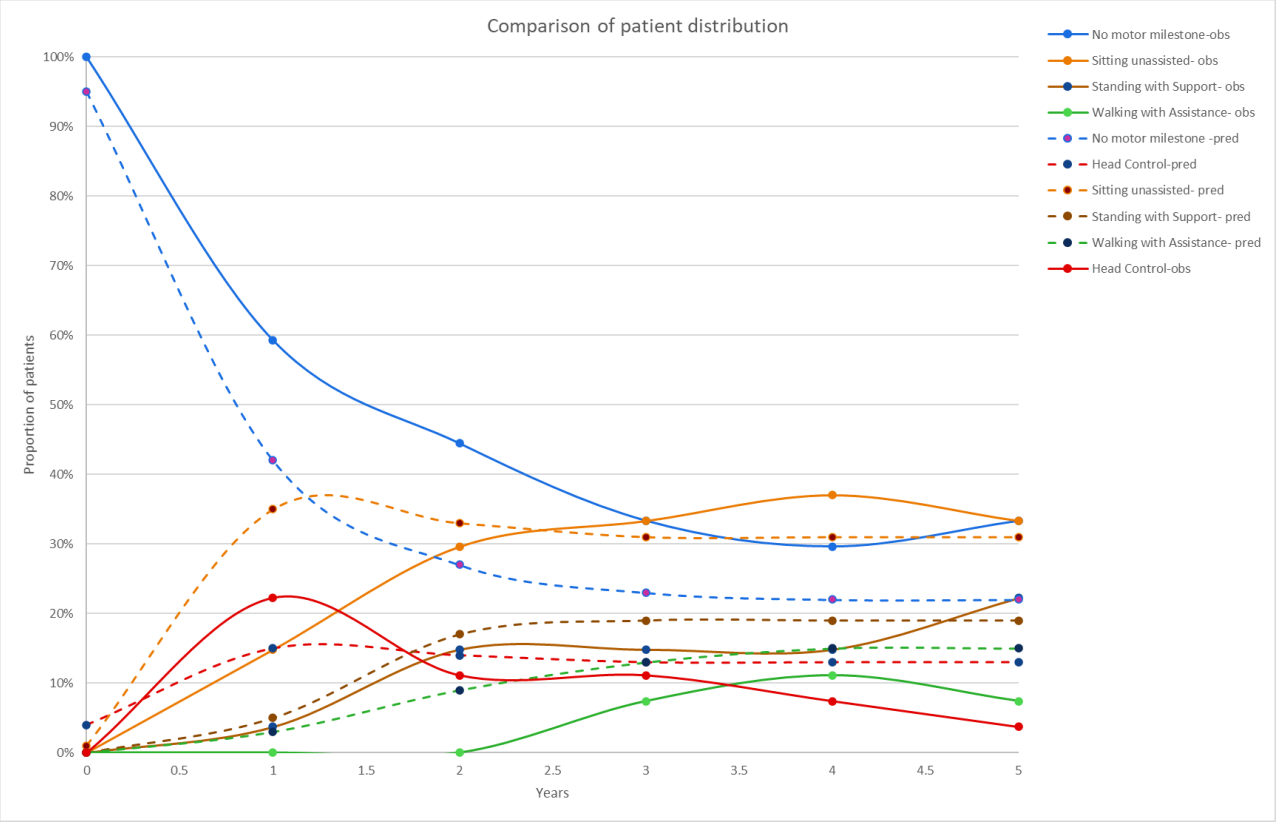


Figure 4 Comparison of patient distribution across motor milestone health states as estimated in the company's base case (using PDMS-2 scores) and scenario analysis (using observed values based on naïve analysis)- eladocagene exuparvovec arm

4.2.6.1.2 Best supportive care

To inform the patient distribution across the motor milestone health states for the best supportive care arm, the company used the NHDB database (see Section 3.5 for a description of the NHDB).

Briefly, the database identified 237 patients with AADC deficiency, of whom 49 had the severe phenotype (achieved no motor milestones by 2 years of age) and had not been included in the eladocagene exuparvovec studies. The set of 49 patients informed the patient distribution in the best supportive care arm. Of these 49 patients, only two

experienced some motor development: one patient achieving the 'walking with assistance' state and the other patient rolling from side to side. The company argue that this finding was consistent with that from Hwu et al.[35] which indicated that only 2% of patients achieve any motor milestone.

At model entry, all patients are assumed to be in the 'no motor milestone' health state. Only a small proportion of patients was assumed to achieve motor milestone improvements by year 5, after which motor milestones remain fixed (due to limited follow-up data beyond this point). Furthermore, the company assumed a linear improvement in motor milestone if a patient in the NHDB jumped more than one motor milestone between observations.

The proportions of patients across the health states used in the base case model for the development phase are shown in Table 25. These estimates are based on the company's naïve analysis (CS Section B.2.9.6).

Table 25: Proportion of patients in the best supportive care arm used in the company base case (based on NHDB database)

Years	None (%)	Head Control (%)	Sitting unassisted (%)	Standing with Support (%)	Walking with Assistance (%)
0	100%	0%	0%	0%	0%
1	98%	0%	2%	0%	0%
2	96%	2%	0%	0%	2%
3	96%	0%	2%	0%	2%
4	96%	0%	2%	0%	2%
5	96%	0%	2%	0%	2%

Source: reproduced from the economic model and CS Table 29 and Table 42

EAG conclusions: Despite the limitations of the methodology of the NHDB (as discussed earlier in Section 3.3.2), we agree with the company decision to use this database for the best supportive care arm given the lack of trial data. Furthermore, our clinical expert indicated that the proportions of patients across the motor milestone states in Table 25 are reflective of those seen in practice. Lastly, this approach is consistent with that adopted in previous HST (HST 2).

4.2.6.2 Survival

The company modelled survival based on motor milestone health states. Mortality data based on the proxy condition cerebral palsy (CP) was used to inform survival estimates for patients with AADC deficiency. The justification for this approach is:

- There are limited published data on patient mortality in AADC deficiency. For example, neither of the two deaths out of 28 patients treated with eladocagene exuparvovec were considered treatment-related (See CS Section B.2.10.7).
- Patients with AADC deficiency normally die prematurely from comorbidities (such as motor dysfunction, multiple organ failure, pneumonia, acute complications during an oculogyric crisis episode and asphyxia) within the first decade of their lives.[24,36] The risk of these comorbidities, and therefore the risk of survival, is expected to vary by motor milestone state.

The company mapped survival estimates for cerebral palsy to AADC deficiency motor milestone health states in their model based on a study by Brooks et al[33]. This California-based study was deemed appropriate for use due to its large sample size (N=16,440 of 4 years old); long-term follow up of 28 years (from January 1983 to December 2010); and its previous use as a source of mortality estimates in a cost-effectiveness model for a 2018 NICE guideline on the management of abnormal muscle tone (dystonia).

We present the company's mapping of motor milestones in AADC deficiency to cerebral palsy motor milestones in Table 26. The survival probabilities of the patients with cerebral palsy in each motor milestone health state are reported in CS Table 43. As these probabilities were reported at five time points for 4-year-olds (i.e., 10, 15, 20, 25 and 30 years), parametric survival curves were fitted to extrapolate survival data for each motor milestone. The model assumed 100% survival up to age 4 years (i.e., at the model entry). Background mortality was appropriately adjusted for general population mortality in England and Wales based on estimates from the Office for National Statistics.

For their base case, the log-logistic curve was chosen for: no motor function; full head control; sitting unassisted; and standing with support, and the exponential curve for walking with assistance. We reproduced the company's survival curves for each AADC deficiency motor milestone health states in Figure 5.

The company also reported the results from their scenario analyses around the survival curves. For further details, see Table 22 from the company's response to EAG clarification question B5.

Table 26: Company's mapping of cerebral palsy motor milestones to AADC deficiency

Motor milestones in cerebral palsy	Motor milestones in AADC deficiency
Tube-fed patients who did not lift their heads in prone position	No motor function
Patients who were able to 'lift head but not the chest in the prone position'	Full head control
Patients who were able to 'lift head and chest, partial rolling'	Sitting unassisted
Patients who were able to 'roll head fully but unable to walk unaided'	Standing with support
Patients who were classified as able to 'walk unaided'	Walking with assistance

AADC, aromatic L-amino acid decarboxylase.

Figure 5 Company's base case survival by AADC deficiency motor milestone health states, adjusted for background mortality
Source: reproduced from CS Figure 42

We note that the company conducted a scenario analysis using survival estimates based on spinal muscular atrophy as a proxy condition; this reduced their base case ICER significantly (as discussed earlier). The EAG did not identify any relevant study other than that identified by the company[33] to inform survival estimates of cerebral palsy mapped to motor milestone states in AADC deficiency. We also did not identify any inconsistencies in the survival probabilities reported in Brooks et al. and the economic model. However, our expert advice suggested that there may be uncertainties with respect to mapping of cerebral palsy motor milestone to those in AADC deficiency as some of the health states across the two conditions may not totally equate.

Comparing the survival estimates in patients with cerebral palsy as reported by Brooks et al.[33] to the company's modelled estimates at 10 years, 20 years and 30 years (shown in Table 27) we note that:

- In the short term (at 10 years), the company's base case survival estimates are similar to the observed values from Brooks et al.
- In the medium term (at 20 years), the company's base case estimates across the motor milestone health states are lower than the values reported by Brooks et al.
- In the long term (at 30 years), the company's predicted estimates were significantly lower compared to those from Brooks et al. for 'no motor function', 'full head control', and 'sitting unassisted' whereas the estimates were comparable for better health states i.e., 'standing with support' and 'walking with assistance'.

For long term survival, examining the company's reported goodness of fit statistics and the figure showing survival extrapolations (reproduced in Figure 6 below from Table 21 and Figure 5 of the company's response to clarification question B5) we observe that:

- Both the log-logistic and Weibull distributions provide a good fit to the observed data up to 30 years across the motor milestone health states.
- Using an exponential curve overestimates the survival of patients in the 'walking with assistance' health state.
- There remains significant uncertainty in survival extrapolation beyond 30 years.
- Of the two best-fitting distributions, the Weibull provides more conservative survival estimates in the long term (beyond 30 years), compared to the log-logistic distribution. For clarity and ease of comparison, we present a diagrammatic representation of the survival curves across the motor milestone health states using a Weibull function in Figure 7 below. Extrapolating survival using Weibull projects similar survival in patients in 'standing with support' and 'walking with assistance' beyond 45 years. The EAG are unclear if it is plausible for patients in these two health states to have similar mortality in the long run.

EAG conclusions: We view the company's approach of modelling survival based on motor milestone health states as reasonable, given the scarcity of robust data. This approach is similar to that adopted in a previous NICE HST appraisal-HST 15. We also agree with the company's assumption of using cerebral palsy as a proxy disease for AADC deficiency based on our expert advice**.** The company's base case survival extrapolations (exponential for 'walking with assistance' and log-logistic for the other motor milestone states)

underestimate observed survival from the Brooks et al. study for the less favourable motor milestone states in the medium and long term. We use the exponential distribution for ‘walking with assistance’ and the Weibull distribution for all the other states in the EAG base case and conduct scenario analysis using the Weibull distribution for all the health states (discussed later in Section 6 of this report). There is considerable uncertainty over survival extrapolations beyond 30 years of follow up.

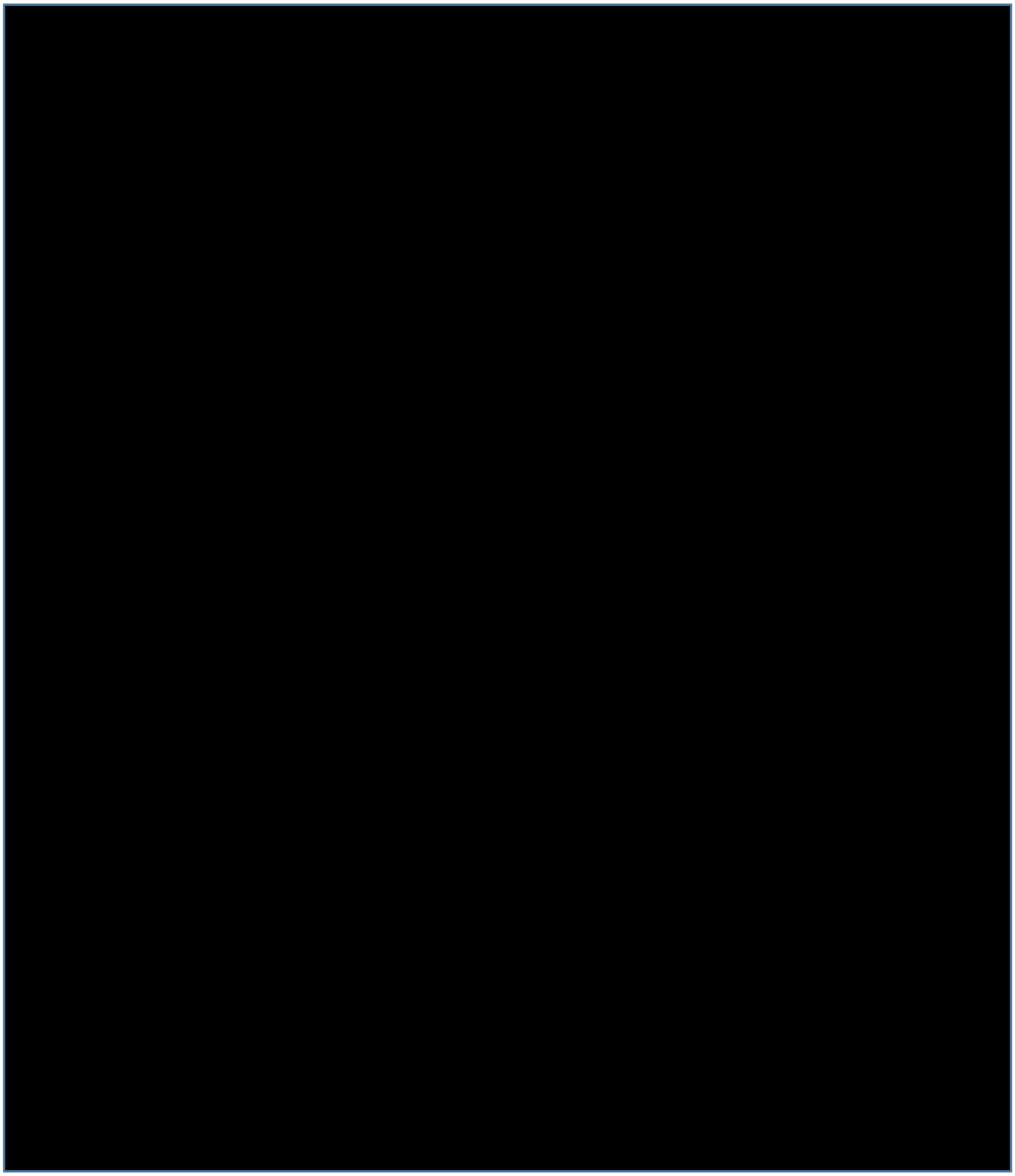


Figure 6 Survival extrapolations for motor milestone health states
Source: reproduced from Figure 5 of the company's response to clarification question B5.
Note: The dotted line represents survival data from Brooks et al.[33]

Figure 7 Estimated survival by AADC deficiency motor milestone health states using Weibull distribution across health states, adjusted for background mortality

Table 27 Comparison of the company's predicted survival estimates with those by Brooks et al

	10 years		20 years		30 years		50 years	
	Company predicted[1]	Observed based on Brook et al.[2]	Company predicted[1]	Observed based on Brook et al.[2]	Company predicted[1]	Observed based on Brook et al.[2]	Company predicted[1]	Observed based on Brook et al.[2]
No motor function	[redacted]	81%	[redacted]	51%	[redacted]	36%	[redacted]	NR
Full head control	[redacted]	87%	[redacted]	66%	[redacted]	47%	[redacted]	NR
Sitting unassisted	[redacted]	92%	[redacted]	79%	[redacted]	57%	[redacted]	NR
Standing with support	[redacted]	98%	[redacted]	93%	[redacted]	86%	[redacted]	NR
Walking with assistance	[redacted]	100%	[redacted]	98%	[redacted]	94%	[redacted]	NR

[1]Company's base case estimates using lo-logistic for 'no motor function', 'full head control', 'sitting unassisted', 'standing with support' and exponential for 'walking with assistance

[2]The observed values from Brookes et al were estimated by the EAG by taking a weighted average approach of the different severity levels within each motor skills (e.g: weighted average of estimates in 'tube-fed', 'fed orally by others' and 'feeds orally self' within "Does not lift head in the prone position")

4.2.6.3 Treatment waning

The company assumed that patients with AADC deficiency will continue to receive treatment benefit of eladocagene exuparvovec throughout their lifetime. They justify their assumption in response to clarification question B6.

EAG conclusions: Consultation with our clinical expert suggests that there is uncertainty regarding persistence of treatment effect in the long term due to lack of longer follow up data. We also note that in a previous NICE HST-15, a pessimistic scenario was conducted where patients with spinal muscular atrophy, a proxy disease to AADC deficiency, were assumed to regress from higher to lower functioning health states after 25 years of treatment. We conducted similar conservative exploratory scenarios to test the impact on the cost-effectiveness results, should the treatment effectiveness wane in the long-term horizon (see Section 6 of this report).

4.2.7 Health related quality of life

4.2.7.1 Health state utilities

The company explain their approach for estimating utilities in CS Section B.3.4 and in their responses to clarification questions B7, B8 and B9. Table 28 below summarises the health state utilities used in the company's base case.

Table 28 Utility values in the company's original and revised base case analyses

Motor milestone health state	TTO utility values
No-motor function	0.494
Full-head control	0.537
Sitting unassisted	0.631
Standing with support	0.676
Walking with assistance	0.728

Source: Reproduced from CS Table 47; TTO: Time Trade off; the estimates are obtained from Smith et al.2021[37]

Owing to a lack of HRQoL and utility data in patients with AADC deficiency, the company developed motor milestone health state vignettes and elicited utilities using various methods including time trade-off (TTO), standard gamble (SG) and discrete choice experiments (DCE). These vignettes were aligned with the motor milestone health states used in the economic model. For their base case, they elicited utilities using TTO in the general UK population (CS Section B.3.4.5.2).

As reported by Hanbury et al.[38] five motor milestone health state vignettes associated with AADC deficiency from a parent/caregiver perspective were devised. Each vignette described symptoms associated with AADC deficiency, i.e., hypotonia, oculogyric crises, motor impairment, dystonia, feeding and swallowing difficulties, mental impairment, irritability, sleep, and autonomic dysfunction. To inform their vignettes, a pragmatic literature review was conducted and held discussions were held with three parents/caregivers from the USA. A 'symptom matrix' was developed to summarise the symptoms and their severity, which in turn, informed the development of motor milestone health state vignettes. Symptoms in the five-motor milestone health state vignettes (as stated above) were assumed to improve globally with improving motor function. The symptom matrix and vignettes were each reviewed and validated by three caregivers and clinicians. These five vignettes were then used to elicit utility values through a TTO study involving 1,598 UK adults from the general population.[37] Of these, 1,039 were reported to provide congruent responses which were used in the TTO study.

The company conducted scenario analyses with the utility values obtained from SG and DCE elicitation methods, shown below in Table 29. Using these utilities reduced the base case ICER of eladocagene exuparvovec versus best supportive care from [redacted] to [redacted] (SG), [redacted] (DCE Scenario 1) and [redacted] (DCE Scenario 2).

Table 29 Utilities for company's scenario analyses

Motor milestone health state	SG utility values	DCE scenario 1 utility values	DCE scenario 2 utility values
No-motor function	0.563	0.494	0.494
Full-head control	0.573	0.536	0.586
Sitting unassisted	0.671	0.629	0.785
Standing with support	0.710	0.700	0.940
Walking with assistance	0.749	0.728	1.000

Source: Company's economic model; SG: Standard gamble; DCE: Discrete Choice experiments

EAG conclusions: We agree with the company's statement that due to the rarity of the condition, together with a very small sample size particularly in paediatric population, robust HRQoL data obtained from preference-based measures is lacking in the literature. The study by Hanbury et al. was conducted to address this gap to inform HRQoL data for economic evaluation in patients with AADC deficiency. Development of the symptom matrix and draft vignettes were based on discussions with a very small sample (n=3) of parent/caregiver

based in the USA, although it is stated that a UK clinician was involved to review and validate the vignettes.

The EAG validated the vignettes with our clinical expert who suggested that while some symptoms (e.g. hypotonia) correlated well to motor milestone achievements, others did not. For example, oculogyric crises may be evident in 'walking with assistance' whereas not all children in this state will have speech. Furthermore, they may also have dystonia. Based on this, we conclude that there may be some uncertainties with respect to how well the vignettes developed by Hanbury et al. link to each motor milestone achievement state to capture the condition, and hence the utilities estimates.

We agree with the company's approach to use TTO over SG and DCE as this aligns with recommendation in the NICE Health Technology Evaluations Manual 2022 and the NICE DSU TSD11. The EAG checked the company's searches for HRQoL studies for patients in AADC deficiency in CS Appendix H and did not identify any other potentially relevant studies. We note that the study by Buesch et al. 2021[39] also reported health state utilities (shown in Table 30) using TTO for 1598 UK participants, although 37% of these responses were incongruent. We conduct a scenario analysis using these estimates in EAG analyses (see Section 6). Furthermore, we also explore the impact on the overall cost-effectiveness results from using the utility estimates from previous NICE appraisal (HST-15) on the proxy condition- spinal muscular atrophy. For further details, see Section 6 of this report.

Table 30 Utility estimates from other sources used in EAG scenario analyses

Using the estimates from Buesch et al.[39]	
Health state	**Utilities**
Bedridden	0.42
Head control	0.48
Sitting unsupported	0.58
Standing with assistance	0.63
Walking with assistance	0.67
Using the estimates from HST-15 based on spinal muscular atrophy[32]	
Health state	**Utilities**
Permanent assisted ventilation	0.00
Not sitting	0.19
Sits unassisted	0.60
Walks unassisted	General population using Ara & Brazier

4.2.7.2 Adverse events disutilities

The company included moderate-to-severe treatment-emergent adverse events (TEAEs) affecting ≥20% of patients within the first 12 months of follow-up, which were assumed to

last up to 60 days. TEAEs were not applied to the best supportive care arm. A study by Sullivan et al.[40], that reported a catalogue of UK-based EQ-5D values for a range of health conditions, was used to inform TEAE disutilities by making several assumptions as described in Table 15 in the company's response to EAG clarification question B2.

The annual rates of TEAEs for patients in the eladocagene exuparvovec arm are reported in CS Table 45 and their associated disutilities in CS Table 46, respectively. A scenario analysis was conducted in response to EAG clarification question B2 which included moderate-to-severe treatment-emergent adverse events (TEAE) affecting ≥5% of patients. The annual rates used in the scenario analysis are reported in Table 14, TAES disutilities in Table 15 and their associated costs in Table 16 of the company's response to EAG clarification question document. As anticipated, including TEAEs affecting ≥5% of patients did not have any significant impact on the overall cost-effectiveness results.

EAG conclusions: In general, the company's approach for modelling TEAE disutilities is reasonable. However, for consistency with previous NICE appraisals, we prefer to include TEAEs affecting ≥5% of patients in our EAG analyses, as shown in Section 6 of this report.

4.2.7.3 Caregiver's quality of life

Carer's disutility was included in the economic analysis (see Table 31). These values are obtained from an observational study in multiple sclerosis that informed a previous NICE HST appraisal- HST 2.[41] Multiple sclerosis motor milestone severity levels were mapped to AADC deficiency motor milestone health states (shown in Table 31). No disutility was assumed for 'walking with assistance'. The company also conducted two scenario analyses: i) using estimates from the study by Gani et al.[42] which used caregiver EQ-5D disutility, originally obtained from carers of patients with Alzheimer's disease; and ii) assuming no carer's disutility.

Table 31 Caregiver disutility values

MS health state	Corresponding AADC deficiency motor milestone health state	Base case disutilities (Acaster et al.)	Scenario disutilities (Gani et al)	Scenario included in the model (QoL study on AADC deficiency caregiver)
Bedridden state	No motor function	0.09	0.11	0.08
	Full head control	0.09	0.11	0.08
Wheelchair/scooter state	Sitting unassisted	0.03	0.05	0.08
	Standing with support	0.03	0.05	0.00

-	Walking with assistance	0.00	0.00	0.00

Reproduced from CS Table 48 and company's economic model

EAG conclusions: The study by Tai et al.[1] retrospectively collected 17 carers' quality of life using the World Health Organization Quality of Life (WHOQOL)-BREF (Taiwan version) and found that Taiwanese carers had improved quality of life after eladocagene exuparvovec. But this isn't used in the company analysis as the study did not provide any disutility estimates.

The economic model also includes carers' disutilities from a QoL study conducted by the company using EQ-5D-5L questionnaire on carers of AADC deficiency patients from Italy, Portugal, Spain and US.[27] However, this study was excluded due to small sample size (initially 12 carers with an additional two added later to the study) leading to suboptimal results. We conduct a scenario analysis using the estimates from this study which increases the company's revised base case ICER for eladocagene exuparvovec versus best supportive care from [redacted] to [redacted]. For further information, see EAG analyses in Section 6.

4.2.7.4 Number of caregivers

With respect to the mean number of caregivers required to support patients with AADC deficiency, the company assumed similar numbers as in spinal muscular atrophy for the most severe state, i.e. the no motor function health state. Their base case analysis assumed that improvement in motor function led to a linear decline in the number of caregivers required. We reproduced the number of caregivers used in the company's analysis in Table 32 below. They also applied a caregiver bereavement disutility value of 0.037, obtained from NICE HST 7 for Strimvelis,[43] to capture the impact of caring for a child with AADC deficiency.

Table 32 Number of primary caregivers associated with each motor milestone state

AADC deficiency motor milestone health state	Number of primary caregivers
No-motor function	2.2
Full-head control	1.9
Sitting unassisted	1.6
Standing with support	1.3
Walking with assistance	1.2

Reproduced from CS Table 49

EAG conclusions: Based on consultation with our clinical expert, we agree with the company's underlying assumption that the number of carers is dependent on the health state. We view that both spinal muscular atrophy and cerebral palsy provide useful comparisons. Our expert suggested that patients in the 'no motor function' state would require two to three unpaid carers, on average, whereas most of the patients in the remaining less severe states would have, on average, two unpaid carers. The EAG included this assumption in our preferred analyses in Section 6. Finally, while the economic model includes unpaid carers, our expert indicated that some of the patients may have paid carers, depending on their circumstances. However, we do not explore this assumption in our EAG analyses.

4.2.8 Resources and costs

The economic model includes costs for acquisition, administration, and monitoring for eladocagene exuparvovec and best supportive care; health state costs; and treatment of adverse events (CS Section B.3.5). The CS reported that a systematic literature review was conducted to identify costs and resource use (CS Appendix I).

4.2.8.1 Drug acquisition and administration costs for eladocagene exuparvovec

Drug acquisition cost for eladocagene exuparvovec is summarised in CS Section B.3.5.1.1.1; and administration and monitoring costs are summarised in CS Section B.3.5.1.1.2 and CS Table 51 and summary of annual costs associated with the intervention in CS Table 56.

EAG conclusions: We have reservations about the resource use assumptions for pre- and post-administration of eladocagene exuparvovec. They assumed that administration of eladocagene exuparvovec through bilateral intraputaminal infusion would be conducted in a day case setting, as in the case of intracranial injections for SMA patients. While the surgery may be performed in a day, post-surgery patients stay in hospital for longer than a day after surgery, they are kept in intensive care for at least two days before moving to a ward where they stay between five to seven days.

Consultation with our clinical expert suggests that in addition to the first MRI scan, patients have a second detailed MRI and an MRA scan prior to surgery. Furthermore, a CSF lumbar puncture is performed to measure serotonin and dopamine metabolites, along with a FDOPA PET scan to image the AADC enzyme.

Post-surgery, the paediatric intensive care unit stay should be costed, on average, for at least two days in intensive care and the paediatric ward stay for five days, to reflect clinical practice, as stated above. We agree with the company's assumption of 8 visits with the multi-disciplinary team. However, our expert advised that patients do not have a CT scan at this point. Instead, two post-operative MRIs would be conducted: one after surgery and another in the longer-term at around 18 months. Furthermore, a post-operative PET scan (as included by the company) does not reflect clinical practice. A FDOPA PET scan, which is more expensive compared to PET scan, is conducted to compare the image of the AADC enzyme at the baseline (pre-operation) to within three months post-operatively and another is carried out at two to three years. For clarity we compare the resources use and their frequencies as reported by the company and as advised by our clinical expert in Table 33. We conduct EAG scenarios using the estimates based on our expert's advice (see Section 6).

Table 33: Pre and post administration resource use and costs associated with administration of eladocagene exuparvovec

Resource use	Frequency assumed by company	Frequencies based on EAG's clinical opinion
Pre-operative resource use		
MRI scan	2	2
MRA	0	1
Lumbar puncture	0	1
FDOPA PET scan	0	1
Post-operative resource use		
Paediatric intensive care unit (per stay)	1	at least 2 days
Paediatric ward stay (per stay)	1	Between 5-7 days
Multidisciplinary team follow-up visits post-surgery	8	8 (2-3 times in the 1st month and thereafter at least 5-6 visits in the 1st year)
CT scan	3	0
PET scan	2	0
FDOPA-PET scan	0	1
Lumbar puncture	1	1

Source: reproduced in part from CS Table 51.

4.2.8.2 Drug acquisition and administration costs for best supportive care

As no disease-modifying treatments are licensed for patients with AADC deficiency, the company included symptomatic treatments, support from a multidisciplinary team of specialists, and medical and technical procedures as part of best supportive care (discussed in CS Section B.3.5.1.2).

The company used a consensus guideline for the diagnosis and treatment of the condition to inform the treatment doses in the best supportive care basket. An overview of the dosing regimens along with the attached weights are summarised in CS Table 52, and the unit

costs in CS Table 53. The resources used as part of multidisciplinary team of specialists for managing people with this condition are summarised in CS Table 54, resources used for medical and technical procedures are in CS Table 55, and a summary of annual costs associated with best supportive care in CS Table 56.

EAG conclusions: The company appropriately applied best supportive care treatments, resource use and medical and technical procedures for both the best supportive care arm and the eladocagene exuparvovec arm in the economic model. We identified a few errors in the company's cost estimation. These are: i) inaccurate assumptions for the unit costs for upper limb splints, lower limb splints, and verticalizers; ii) inaccurate dosage for pramipexole; and iii) inclusion of dietary supplements "Ensure Plus Advance" for children with AADC deficiency. The company addressed these errors as part of their responses to EAG clarification questions B12, B13 and B14, respectively. Correcting these errors had minimal impact on the overall cost-effectiveness results.

4.2.8.3 Health state costs and resource use

In the company's model, best supportive care treatment and resources use are based on motor milestone health state. The proportions of patients treated with the treatments in the best supportive care basket per motor milestone state are summarised in CS Table 57; the annual number of resources used (including follow-up visits, hospitalisation and A&E attendance inputs) by motor milestone health state in CS Table 58; resource inputs for medical and technical procedures per motor milestone health state in CS Table 59 and those for technical procedures in CS Table 60 respectively. They assumed equal number of resources used for both the intervention and comparator arms.

EAG conclusions: Our expert noted several discrepancies in the company's inputs. These are summarised below.

Proportion of patients receiving best supportive care treatments in UK clinical practice

- All patients are likely to receive dopamine agonists and vitamin B6 whereas clonidine is not used.
- More patients are expected to receive benzodiazepines compared to those reported by the company, along with a higher usage of melatonin in patients to address sleep problems.
- It is expected that approximately a quarter of patients would need anticholinergic agents.

- L-DOPA is not used in UK clinical practice. Patients are given folinic acid, not folic acid.
- Patients would receive dietary supplements and vitamin D; all patients receive vitamin D as it is recommended for non-mobile people in general.

We have summarised the above in
Table **34** below and include these assumptions in EAG analyses in Section 6

Table 34: Proportion of patients treated with each treatment category in the best supportive care basket per motor milestone state (based on EAG expert advice)

	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Dopamine agonists	100%	100%	100%	100%	100%
MAO inhibitors	100%	100%	100%	100%	100%
Vitamin B6	100%	100%	100%	100%	100%
Anticholinergic agents	25%	25%	10%	10%	10%
Benzodiazepines	50%	50%	40%	40%	40%
Melatonin	50%	50%	40%	40%	40%
Clonidine	10%	10%	10%	10%	10%
L-Dopa	0%	0%	0%	0%	0%
Folinic acid (vitamin B9)	100%	100%	100%	100%	100%
Dietary supplement	30%	30%	30%	30%	30%
Vitamin D	100%	100%	100%	100%	100%

Source: this is an adjusted version of CS Table 57, but with proportions adjusted to reflect clinical advice received by the EAG.

Resource use

After consultation with our clinical expert, we agree with the company's assumptions for most of the resource use, except the following:

- Patients are likely to have one to two dietician appointments per year and 2 to 3 appointments with a nurse in the 'no motor function' health state.
- The visits to occupational therapy and a physiotherapist assumed by the company are significantly higher than clinical practice. Also, the number of hospitalisations is an over-estimate. Our expert indicated that the hospitalisation and A&E visits are similar.
- Patients are also likely to visit an ophthalmologist one to two times a year. Some patients are likely to be referred to an otolaryngologist.
- Patients are likely to visit pulmonologists twice per year.

The above estimates are summarised in
Table 35 and applied in EAG analysis in Section 6.

Table 35: Annual number of follow-up visits, hospitalisation, and A&E attendance inputs for each health state (based on EAG expert advice)

Resource use	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Dietician	2	2	1	1	1
Endocrinologist	0.00	0.00	0.00	0.00	0.00
Gastroenterologist	2.50	2.50	2.08	1.65	1.65
General practitioner	2.13	2.13	1.79	1.45	1.45
Geneticist	0.00	0.00	0.00	0.00	0.00
Neurologist	2.50	2.50	2.08	1.65	1.65
Nurse	2.5	2.00	1.0	1.0	1.0
Occupational therapy	28	28	22.23	15	15
Ophthalmologist	1.5	1.5	0.43	0.10	0.10
Orthopaedic surgeon	0.13	0.13	0.16	0.20	0.20
Otolaryngologist	1.00	1.00	0.5	0.5	0.5
Paediatrician	1.50	1.50	1.55	1.60	1.60
Physiotherapist	60	60	50	30	30
Pulmonologists	2.0	2.0	1.0	0.00	0.00
Psychiatrist	0.50	0.50	3.33	6.15	6.15
Psychologist	0.00	0.00	0.00	0.00	0.00
Speech therapist	16.31	16.31	26.35	36.40	36.40
Hospitalisation	0.75	0.75	0.60	0.50	0.50
A&E attendance	0.75	0.75	0.60	0.50	0.50

Source: this is an adjusted version of CS Table 58, but with the number of follow-up visits, hospitalisations and A&E attendance adjusted to reflect clinical advice received by the EAG.

For medical and technical procedures, our expert noted that:

- People in the no motor function or full head-control health states may need a barium swallow test.
- Patients in the no motor function state are likely to have 1-2 blood test per annum.
- As above, folic acid and prolactin are not used.
- Patients are unlikely to have 'glycaemia NT dosage in CSF' resource use and annual lumbar punctures are not carried out in the UK clinical practice.
- Urine vanillactic acid level tests are not routinely performed; these are only performed at diagnosis.
- Hip and spine x-rays are performed 6-monthly, depending on the child.

The above estimates are summarised in Table 36 and applied in EAG analysis in Section 6.

Table 36: Medical procedure annual resource use by motor milestone health state (based on EAG expert advice)

Medical procedure	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Barium swallow test	1	1	0.09	0.00	0.00
Blood test	1.5	0.88	0.87	1.00	1.00
Coagulation test (PT, INR, PTT)	0.75	0.75	0.73	0.90	0.90
Electroencephalography	0.75	0.75	0.75	0.75	0.75
Folinic acid dosage in CSF	0.00	0.00	0.03	0.03	0.03
Glycemia NT dosage in CSF	0.00	0.00	0.00	0.00	0.00
Iron dosage	0.88	0.88	0.87	1.00	1.00
Lumbar puncture	0.00	0.00	0.00	0.00	0.00
MRI (cerebral)	0.35	0.35	0.26	0.15	0.15
ECG	0.75	0.75	0.88	1.30	1.30
Non-Bruininks-Oseretesky test	0.00	0.00	0.00	0.00	0.00
Plasma AADC dosage	0.00	0.00	0.00	0.03	0.03
Prolactin dosage	0.00	0.00	0.00	0.00	0.00
Urine test	0.75	0.75	0.81	1.00	1.00
Urine vanillactic acid level	0.00	0.00	0.00	0.00	0.00
X-ray (hip)	2	2	2	0.00	0.00
X-ray (pelvis)	0.25	0.25	0.13	0.00	0.00
X-ray (spine)	2	2	2	2	2

Source: this is an adjusted version of CS Table 59, but annual resource use adjusted to reflect clinical advice received by the EAG.

4.2.8.4 Adverse events

Costs related to moderate-to-severe TEAEs are included in CS Table 61 and in response to clarification question B2. We agree with the company's estimates.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company report their original base case cost-effectiveness results in CS Table 67 and Table 68. The latter and all other cost-effectiveness results in this report are conducted with a Patient Access Scheme (PAS) price discount for eladocagene exuparvovec. In their response to clarification questions B2, B12 to 14 and B19 to 21, the company provided results for a revised base case, which includes changes to estimates for costs and disutilities to correct errors in the original model.

Table 37 and Table 38 present the revised base case results using the list price and PAS price of eladocagene exuparvovec, respectively. The results show that eladocagene exuparvovec offers a mean QALY gain of [redacted] for an additional mean cost of [redacted] (list price) and [redacted] (PAS price) versus best supportive care, giving ICERs of £176,617 and £[redacted] per QALY gained respectively. At a willingness to pay threshold of

£100,000 per QALY, eladocagene exuparvovec results in a negative net health benefit of £13.75 (list price) and [redacted] (PAS price).

The company applied a QALY modifier factor of [redacted] as their undiscounted incremental QALY gain per patient from eladocagene exuparvovec versus best supportive care over a lifetime horizon was between 10 and 30 years. The modifier factor was estimated following NICE guidance presented in the NICE and NHS England consultation document (March 2017) on changes to the arrangements for evaluating and funding drugs and other health technologies assessed through NICE's technology appraisal and highly specialised technologies programmes.[44]

Table 37 Company's revised base case results (discounted at 1.5%, QALY modifier [redacted] applied, list price of eladocagene exuparvovec)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,617	-13.75

Source: reproduced from Table 29 of the company's response to clarification questions.
[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 38 Company's revised base case results (discounted at 1.5%, QALY modifier [redacted] applied, PAS price of eladocagene exuparvovec)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: reproduced from Table 30 of the company's response to clarification questions.
[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

The company did not provide revised scenario and sensitivity analyses conducted on their revised base case cost-effectiveness model. We have therefore conducted these analyses, which are presented throughout section 5.2 of this report. We note that results based on the revised base case are similar to those based on the original base case

5.2 Company's uncertainty analyses

5.2.1 Deterministic sensitivity analyses

The company report results from their deterministic sensitivity analyses on their original cost-effectiveness model in CS Figures 51 to 53 and Table 74 (list price) and CS Figures 54 to 56 and Table 75 (PAS price). The variations in input parameters were based either on 95% confidence intervals or a simple assumed 20% variation, where confidence intervals are unavailable. This applies to patients' characteristics (mean age and weight); efficacy parameter (annual probability of improvement for best supportive care in the development phase); resources used per health state; annual incidences, duration and disutilities of adverse events and health state utilities. We noted that only the health state utilities were varied by the 95% confidence intervals. The results of the sensitivity analyses based on the company's revised model (applied by the EAG) indicate that caregiver disutilities and health state utilities are the main drivers of the model results, although the maximum range of the ICER varies between [redacted] and [redacted] per QALY (using the PAS price).

EAG conclusions: Relevant input parameters such as resources used and costs (including drug acquisition and administration costs, costs for specialist visits, costs of medical and technical procedures and costs of adverse events), efficacy inputs (motor milestone achievement) and survival inputs (parameters from the parametric curves) were excluded from the company's deterministic sensitivity analysis. Inputs for the Bayesian growth curve model were also excluded due to challenges in their implementation. However, scenario analyses were conducted that explored different assumptions related to the efficacy and survival inputs (as discussed in Section 5.2.2).

5.2.2 Scenario analysis

The company reported the results of their scenario analyses in CS Section B.3.11.3 and CS Tables 76 and 77. An additional scenario analysis was conducted as response to EAG clarification question B2. They did not update the results of all the scenario analyses on their revised cost-effectiveness results in their clarification response. We re-ran the company's scenarios on their revised cost-effectiveness model and present the results in Table 39 and

Table 40using the list and PAS price, respectively. We note that the results obtained are very similar to those obtained in their original cost-effectiveness model.

The model results are most sensitive to the use of the QALY modifier, the use of alternative discount rates, alternative utility values, and the use of the motor milestones achievement directly from the observed distributions in the eladocagene exuparvovec trials. The use of a

different model for the Bayesian growth model (asymptotic) and alternative sources for the survival inputs (spinal muscular atrophy) also have a significant impact on the cost effectiveness results.

We report additional EAG scenario analyses in Section 6.1 below.

Table 39 Company's scenario analyses (list price, QALY modifier [redacted] applied, conducted on their revised cost-effectiveness model submitted as response to clarification questions)

Base case setting	Scenario explored	ICER
Base case (revised)	-	**£176,617**
QALY modifier applied	QALY modifier not applied	[redacted]
Discount rate - QALYs: 1.5%, costs: 1.5%	Discount rate - Costs: 0%, QALYs: 0%	[redacted]
	Discount rate - Costs: 3.5%, QALYs: 1.5%	[redacted]
	Discount rate - Costs: 1.5%, QALYs: 3.5%	[redacted]
	Discount rate - Costs: 3.5%, QALYs: 3.5%	[redacted]
Model specification: Gompertz (28 patients)	Model specification: Asymptotic (28 patients)	[redacted]
Length of developmental phase: 12 years	Length of developmental phase: 9 years	[redacted]
Modelling motor milestones through Bayesian growth model	Modelling motor milestones though observed distribution	[redacted]
Development based on NHDB	NHDB-based development: No improvement for patients on BSC	[redacted]
	NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]
Expected survival (Brooks 2014): CP. Best fitting curve: Log-logistic for all health states except walking with assistance [exponential])	2nd best fitting curve overall: Weibull for all health states except walking with assistance (exponential)	[redacted]
	Best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	[redacted]
	Expected survival (Oskoui 2007, Zerres 1997): SMA	[redacted]
Include adverse event (both disutilities and costs)	Exclude adverse events disutilities	[redacted]
	Exclude adverse events costs	[redacted]
	Exclude adverse events disutilities and costs	[redacted]
Source of utility: TTO study (UK)	Source of utility: SG study (UK)	[redacted]
	Source of utility: DCE study (UK), scenario 1	[redacted]
	Source of utility: DCE study (UK), scenario 2	[redacted]
Caregiver disutility applied	No caregiver disutility	[redacted]
Caregiver disutility source: Acaster (2013)	Source of caregiver disutility: Gani *et al.* (2008)	[redacted]
Numbers of caregivers per health state: No-motor function 2.20, Full-head control 1.95, Sitting unassisted 1.70, Standing with support 1.45, Walking with assistance 1.20	2.2 caregivers per health state	[redacted]
TEAEs occurring ≥ 20% of patients	TEAEs occurring ≥ 5% of patients	[redacted]

BSC, best supportive care; CP, cerebral palsy; DCE, discrete choice experiment; ICER, incremental cost-effectiveness ratio; NHDB, natural history database; QALY, quality adjusted life year; SG, standard gamble; SMA, spinal muscular atrophy; TEAEs, treatment emergent adverse events; TTO, time-trade off, UK, United Kingdom

Table 40 Company's scenario analyses (PAS price, QALY modifier [redacted] applied, conducted on their revised cost-effectiveness model submitted as response to clarification questions)

Base case setting	Scenario explored	ICER
Base case (revised)	-	[redacted]
QALY modifier applied	QALY modifier not applied	[redacted]
Discount rate - QALYs: 1.5%, costs: 1.5%	Discount rate - Costs: 0%, QALYs: 0%	[redacted]
	Discount rate - Costs: 3.5%, QALYs: 1.5%	[redacted]
	Discount rate - Costs: 1.5%, QALYs: 3.5%	[redacted]
	Discount rate - Costs: 3.5%, QALYs: 3.5%	[redacted]
Model specification: Gompertz (28 patients)	Model specification: Asymptotic (28 patients)	[redacted]
Length of developmental phase: 12 years	Length of developmental phase: 9 years	[redacted]
Modelling motor milestones through Bayesian growth model	Modelling motor milestones though observed distribution	[redacted]
Development based on NHDB	NHDB-based development: No improvement for patients on BSC	[redacted]
	NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]
Expected survival (Brooks 2014): CP. Best fitting curve: Log-logistic for all health states except walking with assistance [exponential])	2nd best fitting curve overall: Weibull for all health states except walking with assistance (exponential)	[redacted]
	Best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	[redacted]
	Expected survival (Oskoui 2007, Zerres 1997): SMA	[redacted]
Include adverse event (both disutilities and costs)	Exclude adverse events disutilities	[redacted]
	Exclude adverse events costs	[redacted]
	Exclude adverse events disutilities and costs	[redacted]
Source of utility: TTO study (UK)	Source of utility: SG study (UK)	[redacted]
	Source of utility: DCE study (UK), scenario 1	[redacted]
	Source of utility: DCE study (UK), scenario 2	[redacted]
Caregiver disutility applied	No caregiver disutility	[redacted]
Caregiver disutility source: Acaster (2013)	Source of caregiver disutility: Gani *et al.* (2008)	[redacted]
Numbers of caregivers per health state: No-motor function 2.20, Full-head control 1.95, Sitting unassisted 1.70, Standing with support 1.45, Walking with assistance 1.20	2.2 caregivers per health state	[redacted]
TEAEs occurring ≥ 20% of patients	TEAEs occurring ≥ 5% of patients	[redacted]

BSC, best supportive care; CP, cerebral palsy; DCE, discrete choice experiment; ICER, incremental cost-effectiveness ratio; NHDB, natural history database; PAS, patient access scheme; QALY, quality adjusted life year; SG, standard gamble; SMA, spinal muscular atrophy; TEAEs, treatment emergent adverse events; TTO, time-trade off, UK, United Kingdom

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA), with input parameter distributions as reported in CS Table 65. The results, obtained on the company's original cost-effectiveness model, are reported in CS section B.3.11.1 and CS Tables 72 and 73. CS Figures 43 to 50 display the scatterplots and cost-effectiveness acceptability curves and frontier, respectively. The company assigned a normal distribution to age and weight; a gamma distribution for costs, resource use and duration of adverse events; and a beta distribution for adverse event incidence, health state utilities and disutilities.

The company did not update their probabilistic sensitivity analyses for their revised base case produced in response to clarification questions B2, B12 to 14 and B19 to 21. We re-ran the PSA and confirm that the probabilistic results are similar to the deterministic results.

EAG conclusions: As previously identified for the deterministic sensitivity analyses (see section 5.2.1), the company's probabilistic sensitivity analyses do not provide a complete reflection of parametric uncertainty as they did not explore uncertainty related to efficacy and survival estimates.

5.3 Model validation and face validity check

5.3.1 Company's model validation

The company describes their approach to model validation in CS section B.3.14. They reported that the model structure, approaches, inputs, and assumptions were extensively validated through expert advisory boards and clinical surveys, such as:

- Clinical expert advisory board 1 (February 2020) – included five clinical experts with experience managing patients with AADC deficiency.
- Clinical survey (June 2020) – included 25 clinical experts with experience managing paediatric neurometabolic disorders, with most respondents having AADC deficiency experience.
- Economic advisory board 1 (March 2021) – included eight experts with previous experience with economic modelling for rare diseases.
- Clinical expert advisory board 2 (July 2021) – included three clinical experts with experience in managing AADC deficiency in France.
- UK clinical expert consultation (March-April 2022) – included individual consultations with two of the UK's leading clinical experts in AADC deficiency.

The company also conducted internal validation for:

- Gompertz and asymptotic models used in the Bayesian growth curve modelling approach. CS Figure 63 presents the graphical display of the internal validation of the two models against the PDMS-2 scores from the eladocagene exuparvovec clinical trials up to five years post-gene replacement and CS Figure 64 presents data extrapolated up to 10 years. For patients with a 5-year follow up, both models seem to fit the observed data well and generates similar predictions at 10 years. For patients with a shorter follow-up (less than five years), the models fit the observed data in a similar way, but the asymptotic model predicts higher PDMS-2 scores at five and 10 years for most patients.
- The cumulative ordered logit model with PDMS-2 as a covariate using the observed PDMS-2 values, shown in CS Figure 65 up to five years of follow-up and in CS Figure 66 extrapolated to 10 years. The model validates well for all motor milestones and time points up to five years of follow-up, after which the proportion of patients in each motor milestone seem to stabilise. The company points out that the uncertainty of the observed PDMS-2 scores increases over time because of the smaller number of patients at the later timepoints.

EAG conclusions:

- The company conducted an extensive validation with clinical and economic experts to assure the plausibility of the model structure, inputs, and assumptions.
- The EAG agrees with the company's interpretation of the internal validation of the growth curve models against the PDMS-2 scores observed in the eladocagene exuparvovec trials.
- The internal validation of the cumulative ordered logit model against the observed PDMS-2 scores show that the model predictions are more optimistic than the observed values and hence benefit eladocagene exuparvovec, since they predict fewer patients in the severe health states and more patients in the better (less severe) health states.
- However, the company did not provide any information on: i) model quality control (e.g. checking for coding errors, input inconsistencies with source data, etc.); ii) internal validity checks (e.g. comparing model results with outputs from the three clinical trials); and iii) cross-validity checks (e.g. comparing model outcomes with previous NICE appraisals, as relevant).

5.3.2 EAG model validation

The EAG conducted a series of quality checks of the company model. We checked the model for transparency and validity and conducted a range of tests to verify model inputs, calculations, and outputs, such as:

- cross-checking all parameter inputs against values reported in the CS and cited sources;
- checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses;
- checking the individual equations within the model, related to efficacy parameters, estimation of survival calculation, patient trace across the motor milestone health states, total costs, total LYs, and total QALYs;
- manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses;
- applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

The model is generally well-implemented, with some minor errors in parameter inputs and coding. We also spotted a few inconsistencies in parameter values between the CS and the company's model. The company corrected these errors and provided an updated model (as previously mentioned in Section 5.1) in their response to clarification questions B2 (where they updated disutility for pneumonia); B12 (updated costs for upper limb splints, lower limb splints and verticalizers); B13 (updated dosage for pramipexole), B14 (removal of dietary supplement), B19 (exclusion of one-off costs from the follow-up visits with specialists), and updates to parameters and costs highlighted in clarification questions B20 and B21.

The EAG identified four additional errors in the company's revised model, although they have a minor impact in the model results. We discuss these in Section 5.3.3.

Additionally, we are unclear how the observed trial data on motor milestone achievement used in the economic model for the eladocagene exuparvovec arm are derived (model sheet 'Input conversion', cells B310:AC320). This is because:

- We are unable to match the total number of patients and the number of patients in each motor milestone, provided in cells D311:I320 of the model sheet 'Input conversion', with data from the eladocagene exuparvovec clinical trials.

- The EAG are also unable to check the number of participants achieving each motor milestone for the LOCF approach and whether the analysis uses data from all the participants enrolled in the three clinical trials, as only the proportions of patients are available ('Input conversion' sheet, cells Y311:AC320).

5.3.2.1 Internal validity checks

As part of the internal validity checks, we compared:

- the motor milestone achievement observed in the eladocagene exuparvovec trials (using the LOCF) with the company's modelled estimates for eladocagene exuparvovec that uses a Bayesian growth model to predict motor milestone health states. For clarity and completeness, we also provide the estimates obtained from the scenario using the motor milestone achievement measured directly in the eladocagene exuparvovec trials (based on the LOCF approach to impute missing values; last observation defined as the last follow-up visit for each patient) with background mortality and the half-cycle correction applied (see Table 41 below).
- the motor milestone achievement observed in the NHDB with the modelled estimates for best supportive care (see Figure 8 below).
- the survival observed in the cerebral palsy study with the modelled survival for both eladocagene exuparvovec and best supportive care (see Table 27 in section 4.2.6.2**Error! Reference source not found.**).

Eladocagene exuparvovec: motor milestone achievement

The distribution of patients achieving each of the motor milestones in the company's revised base case model is significantly different compared to the distribution of patients observed in the eladocagene exuparvovec clinical trials (using the LOCF approach to impute missing values). The EAG notes that the company's estimates are more optimistic than those observed in the trials, with more patients achieving better health states (such as standing with support and walking with assistance) and fewer remaining with no motor function.

Table 41 Eladocagene exuparvovec: comparison of motor milestone achievement results observed in the clinical trials versus the modelled estimates used in the company's revised base case

Motor milestones	Estimates	Year 1	Year 2	Year 3	Year 4	Year 5
No motor function	Observed trial data (LOCF approach)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's revised base case[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's scenario using observed trial data (LOCF approach)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full head control	Observed trial data (LOCF approach)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's revised base case[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's scenario using observed trial data (LOCF approach)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting unassisted	Observed trial data (LOCF approach)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's revised base case[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's scenario using observed trial data (LOCF approach)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support	Observed trial data (LOCF approach)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's revised base case[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's scenario using observed trial data (LOCF approach)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with assistance	Observed trial data (LOCF approach)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's revised base case[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's scenario using observed trial data (LOCF approach)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Clinical trial values, obtained from CS Table 30 (using the LOCF to impute missing values)
[b] Modelled estimates based on predicted motor milestone achievement using the Bayesian growth curve model and cumulative ordered logit model.
[c] Modelled estimates using the observed trial data on the achievement of motor milestones (based on the LOCF approach to impute missing values; last observation defined as the last follow-up visit for each patient) with background mortality and the half-cycle correction applied.
EAG: Evidence Assessment Group, LOCF, last observation carried forward.

Best supportive care: motor milestone achievement

For best supportive care, Figure 8 shows that the distribution of patients achieving each of the motor milestones used in the model is very similar to the distribution of patients observed in the NHDB (as reported in CS Table 29).

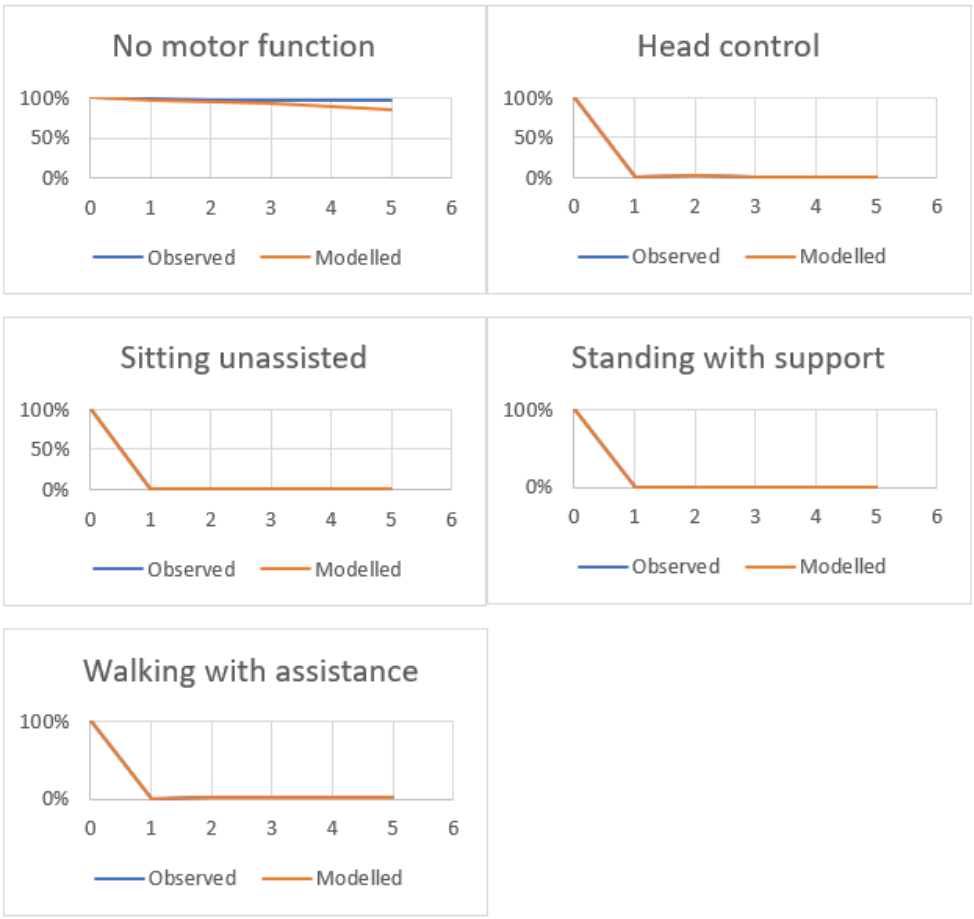


Figure 8 Best supportive care: comparison of motor milestone achievement observed in the NHDB versus modelled estimates
Source: Obtained from CS Table 29; NHDB, natural history database.

Survival

The survival estimates of patients in each of the motor milestones in the company's revised model is generally higher than the estimated survival of patients with cerebral palsy reported in the study by Brooks et al. 2014 (see Table 27 in section 4.2.6.2). The company used the exponential curve to extrapolate data for walking with assistance and Loglogistic for all the other health states.

The EAG notes that the company's estimates are lower than the cerebral palsy values in the no motor function health state but higher in the remaining health states. This is likely to overestimate the survival of eladocagene exuparvovec versus best supportive care as the intervention is assumed to reduce the proportion of patients remaining in the most severe health states and increase the proportion achieving better motor function.

The clinical expert advising the EAG agreed that cerebral palsy and AADC deficiency have

similarities in terms of survival, but she also mentioned that AADC deficiency presents additional risks of mortality, such as oculogyric crises and sometimes unexplained death.

5.3.2.2 Cross validity checks

As part of the cross-validity checks, the EAG compared the health outcomes (life years and QALYs) obtained in previous NICE appraisals with the health outcomes from the company's revised model:

- HST 15 (Onasemnogene abeparvovec for treating spinal muscular atrophy)[32]: this appraisal, which was also used to inform the model structure of the current submission, assessed a gene-replacement therapy in a condition considered as a proxy to AADC deficiency.
- TA588 (Nusinersen for treating spinal muscular atrophy).[45]

The EAG did not find any relevant NICE technology appraisal guidance on cerebral palsy, with the exception of the health economics study attached to the NICE guideline NG62 (cerebral palsy in children and young people under 25 years).[46] However, the NG62 economic study does not report relevant health outcomes to be compared to the current model.

[redacted]*HST 15 (Onasemnogene abeparvovec for treating spinal muscular atrophy)*

We compared the total QALYs (discounted at 3.5%) obtained in the company's updated base case model versus the total QALYs (discounted at 3.5%) reported in HST 15 using the committee's preferred base case (see Table 42 below). It was not possible to compare the life years gained across the two models as those in HST 15 are not publicly available.

On the face of it, the total QALYs yielded by gene-replacement therapies are consistent across the appraisals ([redacted] vs. 9.26). On the contrary, best supportive care yielded lower QALYs in HST 15 than in the company's revised base case model. This might be explained by the assumption that no patients in best supportive care move to better health states (sitting, walking and normal development) in HST 15.

Table 42 Comparison of health outcomes between company's revised model and HST 15 (discounted at 3.5%)

	Intervention	Life years	QALYs
Current model (company)	Eladocagene exuparvovec	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
HST 15 (committee)	Onasemnogene abeparvovec	-	9.26
	BSC	-	0.21
Source: HST 15[32] BSC, best supportive care; HST, highly specialised technology; QALYs, quality adjusted life years.			

[redacted]Table 43 below shows the QALY breakdown per health state in the company's revised base case model and HST 15 (both discounted at 3.5%). Regarding best supportive care, it is clear that no patients moved to sitting, walking and normal development health states in HST 15 contrarily to the current appraisal, in which patients can improve their motor milestones. Regarding the gene-replacement therapies:

- The EAG considers that the non-sitting health state in HST 15 is likely to be the closest health state to both no motor function and full head control health states in the current appraisal. The QALY gain yielded by onasemnogene abeparvovec is lower than eladocagene exuparvovec, which is closely linked to the much lower utility value applied to this health state in HST 15 (0.19).
- The sitting health states also present discrepant QALYs between appraisals, although the utility value applied to this health state in HST 15 (0.6) is very similar to the utility value applied to sitting unassisted in the current model (0.631). Therefore, the lower QALY observed in the company's updated base case model is probably due to a lower proportion of patients or a lower survival in this health state, compared to that in HST 15.
- Walking and normal development health states in HST 15 do not seem reflective of the standing with support or walking with assistance health states in the current appraisal. They reflect more improved health in which patients can walk unassisted or even have a normal development as the general population. This is also highlighted by the fact that general population utilities were applied to these health states in HST 15. However, QALYs were lower for onasemnogene abeparvovec when compared to eladocagene exuparvovec. Fewer patients achieving such improved health states in HST 15 compared to the current model is a potential reason for this finding.

Table 43 QALY breakdown per health state (company's revised model versus HST 15, discounted at 3.5%)

QALYs	Intervention	No motor function	Full head control	Sitting unassisted	Standing with support	Walking with assistance
Current model (company)	Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	**Intervention**	**Permanent ventilation**	**Non-sitting**	**Sitting**	**Walking**	**Normal development**
HST 15	Onasemnogene abeparvovec	0.00	0.55	6.99	0.30	2.37
	BSC	0.00	0.21	0.00	0.00	0.00

Source: HST 15[32]
BSC, best supportive care; HST, highly specialised technology; QALYs, quality adjusted life years.

[redacted]

TA588 (Nusinersen for treating spinal muscular atrophy)

TA588 assesses both early (type 1) and late onset (type 2 and 3) spinal muscular atrophy. We believe that the symptoms of AADC deficiency relate better with the early onset spinal muscular atrophy than with the late onset. However, the EAG considers that comparing the AADC deficiency health outcomes to the early onset TA588 results is not appropriate (see Table 44 below). In the final appraisal determination document of TA588, it is stated that health state and carer utilities are highly uncertain and difficult to quantify.[45]

Table 44 Comparison of health outcomes between company's revised model and TA588 (discounted at 3.5%)

	Intervention	Life years	QALYs
Current model (company)	Eladocagene exuparvovec	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
TA588 (early onset SMA)	Nusinersen	3.98 [a]	-0.96
	BSC	2.32 [a]	-2.34

Source: TA588 [45]
[a] Undiscounted
BSC, best supportive care; TA, technology appraisal; QALYs, quality adjusted life years; SMA, spinal muscular atrophy.

5.3.3 EAG corrections to the company model

The company's model was generally well-implemented, with no substantive errors. As previously stated in section 5.3.2, the company provided a revised model in which errors had been corrected. We identified four additional errors (listed below) in the company's revised model and corrected them.

1. The strength (mg/unit) considered for bromocriptine – should be 2.5mg and not 30mg (company's response to clarification question B21).
2. Inclusion of one-off administration and pre-/post- operative costs as part of the follow-up visits within the specialists' costs – incorrectly included in the 'Cost_calcs' sheet (cells S18:S416). This has been confirmed by the company in their response to clarification questions (company's response to clarification question B19).
3. The formulae to calculate adverse event costs for eladocagene exuparvovec in the 'Cost_calcs' sheet (cells BN17:BR17).
4. The formulas to calculate adverse event costs for best supportive care in the 'Cost_calcs' sheet (cells DZ11:ED11 and CW17:DJ416). We note that this error does not change the company's revised results, since the base case assumes no adverse events for best supportive care.

We present the results from the EAG's corrected company model using the PAS price of eladocagene exuparvovec in Table 45 (discounted at 1.5%), Table 46 (discounted at 3.5%) and Table 47 (discounted at 0%). We note that the results are very similar to the company's original and revised model results (discounted at 1.5%: ICER of [redacted] for EAG's corrected company model versus [redacted] for company's original model versus [redacted] for company's revised model).

Table 45 EAG's corrected company base case results (discounted at 1.5%, QALY modifier [redacted] applied, PAS price of eladocagene exuparvovec)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 46 EAG's corrected company base case results (discounted at 3.5%, QALY modifier [redacted] applied, PAS price of eladocagene exuparvovec)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 47 EAG's corrected company base case results (discounted at 0%, QALY modifier [redacted] applied, PAS price of eladocagene exuparvovec)

Technology	Total			Incremental				
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)	NHB[a]
BSC	[redacted]	[redacted]	[redacted]					
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Willingness to pay threshold of £100,000 per QALY.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

5.3.4 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model and additional analyses is presented in Table 48.

Table 48 EAG summary of key issues and additional analyses

Aspect	Company analyses	EAG analyses (scenarios)	EAG preferred
Model structure and characteristics			
Population	• Age: 4 years • Weight: 11.1 kg • Gender: 50% female	• Age: 2, 6 and 8 years • Weight: 8.5 kg at 2yrs, 15 kg at 6 years, 17kg at 8 years	6 years, 15 kg
Time horizon	• Lifetime	• Scenarios: 10 years, 20 years	--
Discount rates	• Base case: 1.5% for both costs and effects • Scenarios: varying combination of 0%, 1.5% and 3.5%	• No other scenario but results of the EAG analyses presented using 0%, 1.5% and 3.5%.	3.5% for both costs and effects
Duration of development phase	• Base case: 12 years (16 years of age) • Scenario: 9 years (13 years of age)	• Scenarios: 5, 7, 10 and 11 years	--
Efficacy and clinical parameters			
Motor milestones	Eladocagene Exuparvovec • Base case: Bayesian growth models of PDMS2 scores with a cumulative ordered logit model to predict patients' motor milestone achievement • Scenario: Modelling through observed trial distribution, using LOCF	Eladocagene Exuparvovec • Scenarios: i) Modelling using observed trial, based on original sample; ii) Modelling using observed trial, distribution per follow up; iii) using lower and upper confidence interval estimates for the cumulative ordered logit model (0.047 and 0.070)	Modelling through observed trial distribution, using LOCF for missing data imputation

	Best Supportive Care
	• Base case: NHDB
	• Scenario:
	  ○ No improvement
	  ○ 2% improvement in motor milestone state per year in development phase
		Best Supportive Care
		• Annual probability of improvement by a motor milestone during development phase 3% and 5% per year
			--

Aspect	Company analyses	EAG analyses (scenarios)	EAG preferred
Persistence of treatment benefit for eladocagene exuparvovec			
Treatment waning	No treatment waning	Assume treatment waning: • Gradual waning from 25 years • Gradual waning between 25 and 35 years, after which patients are assumed to stay in the same health state • Gradual waning between 25 and 35 years, after which the best supportive care motor milestone achievement is applied • Waning at 25 years at which point the best supportive care motor milestone is applied	--
Survival estimates			
Survival curves for motor milestone health state	Base case: • Exponential for walking with assistance; Log-logistic for others states Scenarios: • Exponential for walking with assistance; and Weibull for others • Loglogistic for 'no motor milestone' and 'full head control', Weibull for 'sitting unassisted', loglogistic for 'standing with support', and exponential for 'walking with assistance' • Expected survival from SMA	Weibull for all health states	Exponential for walking with assistance; and Weibull for all the others
Costs and resource use			

Aspect	Company analyses	EAG analyses (scenarios)	EAG preferred
Costs price year	BNF 2021 prices	Use BNF 2022 prices where available or inflate to 2022 prices	2022 prices
Resource use	CS Tables 51, 57, 58 and 59	Based on EAG expert advice	Estimates based on EAG expert feedback
Utilities and QALY multiplier			
Health state utilities	Base case: • TTO estimates (UK study) Scenarios: • SG estimates (UK study); DCE scenarios 1& 2 (UK)	• Based on the study by Buesch et al. • Based on the estimates used in HST 15 (SMA)	--
QALY multiplier	Applied a modifying factor of 1.709	Agrees with the company's approach; the factor will depend on the undiscounted incremental QALYs from EAG base case	--
Adverse events	Base case: • Included TEAEs affecting ≥20% of patients within the first 12 months of follow-up Scenario: • included TEASs ≥5% of patients within the first 12 months	No additional scenarios	Affecting ≥5% of patients
Carer disutility	Base case: • Carer disutility from Acaster et al. Scenarios: • No carer disutility • Apply carer disutility from Gani et al	Scenario using 'QoL study on AADC deficiency' (included in the economic model)	--
Number of carers	Base case: • CS Table 49 Scenario: • 2.2 carers per each health state	No motor function: 2.5 carers Other motor milestone health states: 2 carers	Yes, same assumption as EAG scenario, i.e.: No motor function: 2.5 carers; Other motor

Aspect	Company analyses	EAG analyses (scenarios)	EAG preferred
			milestone health states: 2 carers.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

We performed a range of additional scenario analyses on the EAG corrected company revised base case model based on the key issues summarised in Table 48 above. Results of these analyses are presented for three discount rates (0%, 1.5% and 3.5%) in Table 49 below; these are based on the PAS price for eladocagene exuparvovec.

Table 49 Additional analyses conducted by the EAG on the EAG's corrected company revised cost effectiveness model (discounted at 0%, 1.5% and 3.5%; QALY modifier [redacted] applied, PAS price for eladocagene exuparvovec)

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
EAG corrected company model	[redacted]	[redacted]	[redacted]
Population: 2 years; 8.5kg	[redacted]	[redacted]	[redacted]
Population: 6 years; 15kg	[redacted]	[redacted]	[redacted]
Population: 8 years; 17kg	[redacted]	[redacted]	[redacted]
Time horizon: 10 years	[redacted]	[redacted]	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	[redacted]
Duration of development phase: 5 years	[redacted]	[redacted]	[redacted]
Duration of development phase: 7 years	[redacted]	[redacted]	[redacted]
Duration of development phase: 10 years	[redacted]	[redacted]	[redacted]
Duration of development phase: 11 years	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on LOCF	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on original sample	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on distribution per follow-up	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: lower CrI for the COLM	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: upper CrI for the COLM	[redacted]	[redacted]	[redacted]
Motor milestone achievement for BSC: improvement of 3% per year	[redacted]	[redacted]	[redacted]
Motor milestone achievement for BSC: improvement of 5% per year	[redacted]	[redacted]	[redacted]
Treatment waning: gradual from 25 years onwards	[redacted]	[redacted]	[redacted]
Treatment waning: gradual between 25 and 35 years (same health state)	[redacted]	[redacted]	[redacted]
Treatment waning: gradual between 25 and 35 years (BSC distribution)	[redacted]	[redacted]	[redacted]
Treatment waning: sudden decline at 25 years (BSC distribution)	[redacted]	[redacted]	[redacted]
Survival extrapolation: Weibull for all health states except walking with assistance (exponential)	[redacted]	[redacted]	[redacted]
Survival extrapolation: Weibull for all health states	[redacted]	[redacted]	[redacted]
Costs: updated prices to 2021/2022	[redacted]	[redacted]	[redacted]
Resource use: EAG expert estimates	[redacted]	[redacted]	[redacted]
Health state utilities from Buesch et al.	[redacted]	[redacted]	[redacted]
Health state utilities from HST 15	[redacted]	[redacted]	[redacted]
Number of carers: 2.5 for no motor function and 2 for the other health states	[redacted]	[redacted]	[redacted]

Carer disutility: 'QoL study on AADC deficiency'	[redacted]	[redacted]	[redacted]

AADC, aromatic L-amino acid decarboxylase; BSC, best supportive care; CrI, credible interval; EAG, Evidence Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; PAS, patient access scheme; QALY, quality adjusted life years; QoL, quality of life.

Using observed trial data based on the original sample to inform patient distribution across the motor milestone health states for eladocagene exuparvovec has the highest impact in the cost-effectiveness results (ICER increases from [redacted] to [redacted] per QALY at a discount rate of 3.5%). Applying a shorter time horizon (10 and 20 years) also influences the cost-effectiveness results (ICER increases from [redacted] to [redacted] and [redacted] per QALY, respectively, at a discount rate of 3.5%) significantly. Other scenarios that influence the base case ICER (at a discount rate of 3.5%) include: exploratory treatment waning assumptions, use of the lower and upper credible interval estimates for the cumulative ordered logit model, alternate estimates for health state utilities (from HST 15 and Buesch et al), using observed trial data (using LOCF approach for missing data imputation and distribution per follow-up) to inform patient distribution across the motor milestone health states for eladocagene exuparvovec, varying discount rates, improvement of 5% per year in motor milestone achievement for best supportive care and using Weibull distribution for survival extrapolation across all the health states. [redacted]

6.2 EAG's preferred assumptions

The EAG preferred model assumptions are as follows:

1. **Baseline age and weight of population**: 6 years and 15 kg
2. **Discount rate of costs and effects**: We prefer a discount rate of 3.5% (more details in section 4.2.5) as opposed to the company's base case which present the results discounted at 1.5%. However, due to the high uncertainty around this assumption, we present the EAG results for the discount rates of 0%, 1.5% and 3.5%.
3. **Motor milestone achievement (eladocagene exuparvovec)**: Use the trial observed distribution of patients across the motor milestone health states using the LOCF approach to impute missing data.
4. **Adverse events**: Occurring in ≥5% of patients in the trial.
5. **Extrapolation of survival curves**: Weibull parametric curve to extrapolate survival in all health states of the model, except for the "walking with assistance" (exponential).
6. **Update costs to the most recent price**: All costs are updated to 2021/2022 prices by using the BNF 2022 prices [2] or inflating based on the PSSRU inflation indices for 2020/2021.[3]
7. **Resource use estimates**: based on estimates informed by the EAG's clinical expert.

8. **Number of carers**: based on our expert's advice, which assume patients in the most severe health state (no motor function) require 2.5 carers while patients in the other health states require two carers.

6.2.1 Results from the EAG preferred model assumptions

Table 50 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the EAG's corrected company base case. Incorporating the EAG's assumptions leads to an increase of the ICER from [redacted] to [redacted] for a discount rate of 0%, from [redacted] to [redacted] for a discount rate of 1.5% and [redacted] to [redacted] for a discount rate of 3.5% respectively, based on the PAS price of eladocagene exuparvovec.

A QALY modifier factor of [redacted] was applied in the EAG base case as the undiscounted incremental QALY gain per patient from eladocagene exuparvovec versus best supportive care over a lifetime horizon is between 10 and 30.

The assumption that has the biggest impact on the cost-effectiveness results is the use of the observed patient distribution across the motor milestone health states (using LOCF approach for missing data imputation) from the three eladocagene exuparvovec trials (ICER increase of [redacted] per QALY, discounted at 3.5%). The assumptions behind discount rate (ICER increase of [redacted] per QALY from a rate of 1.5% to 3.5%) and resource use (ICER increase of [redacted] per QALY, discounted at 3.5%) also significantly change the ICER for eladocagene exuparvovec versus best supportive care. Incorporating the remaining EAG assumptions influence the ICER to a lesser extent.

Table 50 EAG's preferred model assumptions (discounted at 0%, 1.5% and 3.5%, QALY modifier [redacted] applied, PAS price for eladocagene exuparvovec)

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER (£/QALY)		
		3.5%	3.5%	3.5%	0%	1.5%
EAG corrected company base case	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Age and weight: 6 years and 15kg	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Motor milestone achievement: observed data (LOCF)	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Adverse events: ≥5%	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Extrapolation of survival: Weibull + exponential	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Updated costs	BSC	[redacted]	[redacted]			

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER (£/QALY)		
		3.5%	3.5%	3.5%	0%	1.5%
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Resource use estimates: EAG expert	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Number of carers: 2.5 for no motor function and 2 for the other health states	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred base case	BSC	[redacted]	[redacted]			
	EE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC, best supportive care; EAG, Evidence Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; PAS, patient access scheme; QALY, quality adjusted life years.

6.2.2 Scenario analyses conducted on the EAG preferred model assumptions

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some of the model assumptions in the overall cost-effectiveness results. We replicate the company's scenarios, as previously described in section 5.2.2 (Table 51 below) as well as conduct additional scenarios to assess the impact of changing other model assumptions (as shown in Table 52 below).

Similar to what we observe in the company's original scenarios (Table 39 and Table 40) and EAG additional scenarios conducted in the company's revised base case (Table 49), the ICER of the EAG preferred model is most sensitive to the following assumptions: QALY modifier, alternative discount rates, short time horizons, the approach used to distribute patients across motor milestone health states (observed data versus Bayesian growth model), the approach used to impute missing data for the observed distribution of patients across motor milestones (based on LOCF, original sample or distribution per follow-up), exploratory treatment waning assumptions and health state utility values.

Table 51 Company's scenario analyses using the EAG's preferred model assumptions (discounted at 0%, 1.5% and 3.5%; QALY modifier [redacted] applied, PAS price for eladocagene exuparvovec)

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
EAG preferred model	[redacted]	[redacted]	[redacted]
QALY modifier not applied	[redacted]	[redacted]	[redacted]
Bayesian growth model: Asymptotic (28 patients)	[redacted]	[redacted]	[redacted]
NHDB-based development: No improvement for patients on BSC	[redacted]	[redacted]	[redacted]
NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]	[redacted]	[redacted]

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
Survival - best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	[redacted]	[redacted]	[redacted]
Expected survival (Oskoui 2007, Zerres 1997): SMA	[redacted]	[redacted]	[redacted]
Exclude adverse events disutilities	[redacted]	[redacted]	[redacted]
Exclude adverse events costs	[redacted]	[redacted]	[redacted]
Exclude adverse events disutilities and costs	[redacted]	[redacted]	[redacted]
Source of utility: SG study (UK)	[redacted]	[redacted]	[redacted]
Source of utility: DCE study (UK), scenario 1	[redacted]	[redacted]	[redacted]
Source of utility: DCE study (UK), scenario 2	[redacted]	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]	[redacted]
Source of caregiver disutility: Gani *et al.* (2008)	[redacted]	[redacted]	[redacted]
2.2 caregivers per health state	[redacted]	[redacted]	[redacted]
BSC, best supportive care; EAG, Evidence Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years.			

Table 52 Additional scenario analyses using the EAG's preferred model assumptions (discounted at 0%, 1.5% and 3.5%; QALY modifier [redacted] applied, PAS price for eladocagene exuparvovec)

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
EAG preferred model	[redacted]	[redacted]	[redacted]
Population: 2 years; 8.5kg	[redacted]	[redacted]	[redacted]
Population: 8 years; 17kg	[redacted]	[redacted]	[redacted]
Time horizon: 10 years	[redacted]	[redacted]	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: Bayesian growth model (Gompertz)	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on original sample	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on distribution per follow-up	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: lower CrI for the COLM	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: upper CrI for the COLM	[redacted]	[redacted]	[redacted]
Motor milestone achievement for BSC: improvement of 3% per year	[redacted]	[redacted]	[redacted]
Motor milestone achievement for BSC: improvement of 5% per year	[redacted]	[redacted]	[redacted]
Treatment waning: gradual from 25 years onwards	[redacted]	[redacted]	[redacted]
Treatment waning: gradual between 25 and 35 years (same health state)	[redacted]	[redacted]	[redacted]
Treatment waning: gradual between 25 and 35 years (BSC distribution)	[redacted]	[redacted]	[redacted]
Treatment waning: sudden decline at 25 years (BSC distribution)	[redacted]	[redacted]	[redacted]
Adverse events: occurring in ≥20% of patients	[redacted]	[redacted]	[redacted]
Survival: Weibull for all health states	[redacted]	[redacted]	[redacted]
Survival: exponential for walking with assistance; log-logistic for the other health states	[redacted]	[redacted]	[redacted]
Resource use: company's estimates	[redacted]	[redacted]	[redacted]
Health state utilities from Buesch et al.	[redacted]	[redacted]	[redacted]
Health state utilities from HST 15	[redacted]	[redacted]	[redacted]
Carer disutility: 'QoL study on AADC deficiency'	[redacted]	[redacted]	[redacted]

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
AADC, aromatic L-amino acid decarboxylase; BSC, best supportive care; CrI, credible interval; COLM, cumulative ordered logit model; EAG, Evidence Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years; QoL, quality of life.			

6.3 Conclusions on the cost effectiveness evidence

The company's cost-effectiveness analysis presents several limitations intimately related with the ultra-rare nature of AADC deficiency – small sample size of eladocagene exuparvovec trials, lack of published data in AADC deficiency, limited utility, and survival data.

There are a few clinical uncertainties that directly inform the cost-effectiveness model and therefore influence its results. These include:

- The approach to imputing missing values – LOCF – for the motor milestone achievement distribution observed in the eladocagene exuparvovec trials assumes that people's last observed motor milestone achieved is maintained over time. While the EAG accepts this as a reasonable approach, there is a theoretical possibility of decline in motor function (for further discussion, see section 3.2.6). Additionally, it is unclear how much missing data were imputed, which makes it difficult to determine how much it matters if the LOCF assumption is incorrect.
- It is unclear how the observed trial data on motor milestone achievement for eladocagene exuparvovec was derived and input into the economic model. The EAG cannot check the accuracy of the pooled proportions of participants from each trial achieving the motor milestones (further details are in sections 3.2.6 and 5.3.2). It is also unclear whether data from all participants and beyond 12 months for AADC-011 were included in the pooled analyses (more details in section 3.2.6). We use the reported observed trial data (with LOCF approach) in our preferred base case but further clarification from the company would provide clarity on this issue.
- Long-term data for eladocagene exuparvovec beyond five years is uncertain. Numerical results would be useful to validate the distribution of patients achieving each motor milestone used in the model and to further inform the assumption that treatment effect is sustained over time (i.e., that there is no decline in motor milestone achievement at any point over time) (as discussed earlier in section **Error! Reference source not found.**).

The key issues identified by the EAG related to the cost effectiveness evidence are as follows:

1. **It is uncertain whether eladocagene exuparvovec meets the criteria outlined in the NICE manual[34] to apply a non-reference discount rate of 1.5%.** The EAG considers that a discount rate of 3.5% is more appropriate since it is unclear (i) if the technology will restore patients to full or near-full health and (ii) whether the benefits will persist in the long-term. However, as uncertainties remain, we presented the results of the EAG analyses for the discount rates of 0%, 1.5% and 3.5% to illustrate the impact of this assumption on the overall cost-effectiveness results.
2. **The EAG have concerns about the company's approach of using PDMS-2 scores to predict motor milestone achievement** (see section 4.2.6.1.1 for further details on the company's methods) rather than using the data observed directly in the trials due to the following reasons: i) motor milestone achievement is more reflective of how motor function is assessed in NHS practice than the PDMS-2 scores; ii) the prediction of motor milestone achievement through PDMS-2 scores overestimates the effectiveness of eladocagene exuparvovec compared with estimates from observed data (see section 5.3.2.1 and Table 41 above); and, iii) this approach lacks consistency with the approach adopted for the best supportive care arm where the observed values obtained from the company's naïve analysis are used. Therefore, we use the observed data on motor milestone achievement from the eladocagene exuparvovec clinical trials in our preferred base case.
3. **There is uncertainty in the persistence of treatment benefit in the long term.** The EAG notes the lack of long-term data beyond 10 years to inform whether the treatment benefit of eladocagene exuparvovec persists over time or patients decline at any point (see section 4.2.6.3). Therefore, although we assume no treatment waning in our preferred base case, we explore several exploratory scenarios assuming a decline in treatment effect (gradual decline from year 25 onwards, between year 25 and 35 or a sudden decline at year 25).
4. **There is a potential overestimation of survival benefits in people receiving eladocagene exuparvovec.** The company's base case adopted a log-logistic distribution to extrapolate survival in "no motor function", "head control", "sitting unassisted" and "standing with support" health states and exponential for "walking with assistance". The EAG considers that the Weibull distribution provides the best statistical and visual fit to the survival data of all health states (further details are in section 4.2.6.2), although this curve predicts similar survival for patients in the health states "standing with support" and "walking with assistance" beyond 45 years. We are unclear whether this is clinically plausible. Therefore, we used Weibull in our preferred base case for all the health states, except for "walking with assistance" for

which we used exponential but tested the use of Weibull for all health states in a scenario analysis.

5. **It is unclear if the company's resource use estimates are reflective of NHS clinical practice.** The clinical expert advising the EAG identified some discrepancies between the company's resource use estimates and her own experience and expectations in clinical practice including: i) pre- and post-administration resource use related to the administration of eladocagene exuparvovec; ii) use of symptomatic treatments by motor milestone; iii) frequency of attendance of follow-up visits with specialists, hospitalisation and accident and emergency visits by motor milestone; and iv) use of medical and technical procedures by motor milestone. We opted to apply the resource use estimates from our clinical expert in our preferred base case.

The incorporation of the EAG's preferred assumptions in the economic model leads to an increase in the ICER from [redacted] (discounted at 1.5% and using the PAS price of eladocagene exuparvovec) to [redacted] per QALY (discounted at 3.5%) or [redacted] (discounted at 1.5%) using the PAS price. The ICER is most sensitive to changes in assumptions related to the: QALY modifier, alternative discount rates, a shorter time horizon, the approach used to estimate the patient distribution across motor milestone health states (that is, Bayesian growth curve model or observed trial data), the approach used to impute missing data for the observed distribution of patients across motor milestones (that is, based on original sample, distribution per follow up or LOCF), treatment waning and health state utility values.

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8 Appendices

Appendix 1

Searching concerns: the overall search strategy and the wide selection of sources was good, and the EAG believes no relevant studies will have been missed. However, there are issues with the search strings that despite having minimal impact on the search results are documented in Table 53 below for completeness.

Table 53 Issues in the literature search strings

Search issue	EAG comment	Impact on SLR
Errors in search syntax: proximity operator adj8 is used in the intervention/comparator search line but it is invalid for the database platforms that are reported	Searching error	Minimal. Not a huge literature base, and other search terms in the intervention/comparator line were comprehensive.
Search syntax not consistently reported: the population and the intervention/comparator search lines do not report which fields were searched. Although the other search lines for the filters report /de or :ti,ab for most terms they are often not reported for the last search terms in a line.	Reporting omission	Searches are not easily reproducible.
MeSH terms not always used: Embase and MEDLINE searches were performed together on the Embase interface and used the keyword mapping functionality instead of inputting MeSH terms manually; MeSH terms are available in the Centre for Reviews and Dissemination (CRD) databases (i.e. for Health Technology Assessment (HTA)	Not best practice for a *systematic* literature review	Negligible. Database mapping functionality use, and EAG checked for any results using the MeSH AADC heading in the CRD databases.

Database and NHS EED) but the MeSH AADC term was not used.		
Redundant/poor use of search filters in CRD database searches	Not best practice	None

Appendix 2

Table 54 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The search strategies and selection criteria all use a PICOD framework consistently matching the scope in the decision problem. (CS Tables 85-90)
Were appropriate sources of literature searched?	Yes	MEDLINE and MEDLINE In Process, Embase and Embase Classic, Cochrane CENTRAL, HTA Database, NHS EED, ScHARRHUD, and EuroQol; a wide range of grey literature. (CS B.2.1 and D1.1.1)
Was the date coverage of the searches appropriate?	Yes	From database inception to 23 February 2022; the most recent three years for conference proceedings. (CS D1.1.1)
Were appropriate search terms used and combined correctly?	Mostly	Some errors in search syntax with the proximity operator and inconsistent/absent reporting of which fields were searched; MeSH terms not always used – relied on automatic mapping in the Embase interface. Search filters were used but not always cited, and unnecessary for the CRD databases search. Due to these issues the searches are not best practice for a systematic literature review nor are they easily replicable. However the EAG believes this would have minimal impact on the results.

		See also Table 53 of this report for further details.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	CS Table 90 outlines the inclusion and exclusion criteria. They are appropriate and relevant to the decision problem. (CS D1.1.6)
Were study selection criteria applied by two or more reviewers independently?	Yes	In addition, the two reviewers held a discussion after 20% of the papers had been reviewed to ensure their decisions were aligned. A third reviewer was involved with disagreements where required. (CS D1.1.2)
Was data extraction performed by two or more reviewers independently?	No	One reviewer performed data extraction and the second reviewer had a checking role. Discrepancies were resolved by discussion or consultation with a third reviewer. (CS D1.1.3) The EAG finds this acceptable.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes – with some overlap and one exception	The amended version of the CASP checklist for cohort studies, as detailed in the NICE STA guidance for companies, was used to assess the quality of the three interventional trials.[ref] (CS B2.5, D1.3, D1.1.5 and D1.4) The same checklist was used to assess study quality for all 38 included papers individually (of which 23 papers report the three interventional trials). (CS B2.5, D1.1.5 and D1.3) See section 3.2.2 of this report for details. The company did not assess the Natural History Database study, included in the ITC, for quality or risk of bias.

Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	One reviewer performed the quality assessment and the second reviewer had a checking role. Discrepancies were resolved by discussion (clarification response A5).
Is sufficient detail on the individual studies presented?	Yes	CS sections B2.2-B2.6; and the company provided the CSRs and SAPs for each trial. (NB the SAP for AADC-CU/1601 and the study protocols for each trial were supplied in response to clarification questions C4 and C5.)
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	The company attempted to conduct an adjusted ITC, and the EAG deems methods used were appropriate. The ITC and its methods are discussed in sections 3.3 to 3.4 of this report.

Appendix 3

Table 55 AADC-CU/1601 critical appraisal with EAG assessment

Study name: AADC-CU/1601: Compassionate use treatment with eladocagene exuparvovec patients with AADC deficiency				
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**EAG response**	**EAG comments**
Was the cohort recruited in an acceptable way?	Yes	As per clinical trial requirements, set inclusion and exclusion criteria, described in the publication and protocol, were followed.	Yes	Study enrolment required a diagnosis of AADC deficiency per study protocol and the patients represent the relevant population.
Was the exposure accurately measured to	Yes	All 8 patients (100%) received eladocagene exuparvovec treatment. Full details of	Yes	All patients received eladocagene exuparvovec per protocol. Same procedure, 100% compliance.

minimise bias?		interventions and follow-ups are provided.		
Was the outcome accurately measured to minimise bias?	Yes	• All patients (100%) followed-up for primary outcomes up to month 24, 75% followed-up at month 60 and 25% followed-up post 60-months. • Follow-ups for all patients were conducted at voluntary monthly sessions, though a sequential gatekeeping procedure was used for testing at the 60-month timepoint. • Primary outcomes (PDMS-2) and secondary outcomes (AIMS, CDIIT, neurological examinations and pharmacodynamic endpoints) were measured consistently in line with the guidelines	Probably	Blinding to treatment exposure was not possible, however bias was minimised as outcomes were measured using objective, validated measurement tools and follow-ups were carried out per protocol. No centralised assessment or independent clinical verification was reported for any of the outcomes.

		set out in the CSR.		
Have the authors identified all important confounding factors?	Yes	All major influences on outcomes included: baseline characteristics and (age at baseline, PDMS-2 baseline scores, AIMS baseline scores).	Yes	Baseline characteristics of age and measurement scores relating to motor development are identified as potentially confounding. There are no time-varying confounding factors. Any concomitant treatments are for symptoms and do not treat the cause (impact the production of dopamine) and therefore are not confounding factors.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The primary analysis of efficacy does not involve any covariate adjustments. For the secondary endpoint analyses of PDMS-2, AIMS, and CDIIT, the repeated measures models included the covariates of baseline scores, age at the time of eladocagene exuparvovec infusion, and visit.	Yes	As per the company study assessment in the column to the left. No adjustments made for the primary efficacy endpoint Repeated measures models are appropriate.
Was the follow-up of patients complete?	Yes	All 8 patients (100%) completed the follow-up at 24 months. 6 patients (75%) completed the follow-up at month 60.	No	At the primary efficacy analysis timepoint (60 months) only 6 out of 8 patients (75%) completed follow up. For the secondary outcome of oculogyric crisis, AADC-CU/1601 CSR (section 11.4.2.6.1) reports only [redacted]
How precise (for example, in terms of confidence interval and p-values)	Yes	95% confidence intervals used, and P-values provided for primary and secondary endpoints.	Mostly	As per the company study assessment in the column to the left. 95% confidence intervals limited to the primary efficacy (achievement of key motor milestones) and putaminal -specific uptake by PET imaging outcomes only. No 95% confidence intervals or p-values reported for oculogyric crisis

are the results?				

Source: partly reproduced from CS Table 105

Table 56 AADC-010 critical appraisal with EAG assessment

Study name: AADC-010: A phase 1/2 clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC				
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**EAG response**	**EAG comments**
Was the cohort recruited in an acceptable way?	Yes	As per clinical trial requirements, set inclusion and exclusion criteria, described in the publication and protocol, were followed. The demographic and baseline characteristics of the study population were representative of patients with AADC deficiency and clinically consistent with the natural history control group.	Yes	Study enrolment required a diagnosis of AADC deficiency per study protocol and the patients represent the relevant population.
Was the exposure accurately measured to minimise bias?	Yes	All 10 patients (100%) received eladocagene exuparvovec treatment. Full details of interventions and follow-ups are provided.	Yes	All patients received eladocagene exuparvovec per protocol. Same procedure, 100% compliance.
Was the outcome accurately measured to minimise bias?	Yes	• All patients (100%) followed-up for primary outcomes up to month 12, 90% followed-up to month 24, 80% followed-up to month 36, with 50% continuing post 60-months. • Follow-ups for all patients were conducted at equivalent three-monthly sessions for the first year, with voluntary ups every 6-months thereafter. A sequential gatekeeping procedure was used for testing at the 24-month timepoint. • Primary outcomes (PDMS-2) and secondary outcomes (AIMS, Bayley-III, body weight, immunogenicity	Probably	Blinding to treatment exposure was not possible, however bias was minimised as outcomes were measured using objective, validated measurement tools and follow-ups were carried out per protocol. No centralised assessment or independent clinical verification was reported for any of the outcomes.

		endpoints and pharmacodynamic endpoints) were measured consistently in line with the guidelines set out in the CSR.		
Have the authors identified all important confounding factors?	Yes	All major influences on outcomes included: baseline characteristics and demographics (age at baseline, PDMS-2 baseline scores, AIMS baseline scores, Bayley-III baseline scores).	Yes	Baseline characteristics of age and measurement scores relating to motor development are identified as potentially confounding. There are no time-varying confounding factors. [redacted] (AADC-010 CSR Table 9).
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The primary analysis of efficacy did not involve any adjustments for covariates. For the secondary endpoint analyses of motor development (PDMS-2, AIMS, and Bayley-III), the repeated measures models incorporated various covariates, such as baseline scores, age at the time of eladocagene exuparvovec gene-replacement therapy, and visit.	Yes	As per the company study assessment in the column to the left. No adjustments made for the primary efficacy endpoint Repeated measures models are appropriate.
Was the follow-up of patients complete?	Yes	All 10 patients (100%) completed the follow-up at 12 months.	No	At the primary efficacy analysis timepoint (60 months) only 5 out of 10 patients (50%; CS Table 9) or 8 out of 10 (80%; CS Table 14) completed follow up For the secondary outcome of oculogyric crisis, AADC-010 CSR Table 13 reports only [redacted]
How precise (for example, in terms of	Yes	95% confidence intervals used, and P-values provided for primary and secondary endpoints.	Yes	As per the company study assessment in the column to the left.

confidence interval and p-values) are the results?				95% confidence intervals limited to the putaminal -specific uptake by PET imaging outcome only.

Source: partly reproduced from CS Table 106

Table 57 AADC-011 critical appraisal with EAG assessment

Study name: AADC-011: A clinical trial for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency using AAV2-hAADC - an expansion				
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**EAG response**	**EAG comments**
Was the cohort recruited in an acceptable way?	Yes	As per clinical trial requirements, set inclusion and exclusion criteria, described in the publication and protocol, were followed. The demographic and baseline characteristics of the study population were representative of patients with AADC deficiency and clinically consistent with the natural history control group.	Yes	Study enrolment required a diagnosis of AADC deficiency per study protocol and the patients represent the relevant population.
Was the exposure accurately measured to minimise bias?	Yes	All 12 patients (100%) received eladocagene exuparvovec treatment. Full details of interventions and follow-ups are provided.	Yes	All patients received eladocagene exuparvovec per protocol.100% compliance.
Was the outcome accurately measured to minimise bias?	Yes	• The mean follow-up for primary outcomes was 11.1 months. • Follow-ups for all patients were conducted at equivalent three-monthly sessions for the first year, with a voluntary enrolment to a follow-up study thereafter. • Primary outcomes (PDMS-2) and secondary outcomes (PDMS-2, AIMS, Bayley-III) were measured consistently in line with the guidelines set out in the CSR.	Probably	Blinding to treatment exposure was not possible, however bias was minimised as outcomes were measured using objective, validated measurement tools and follow-ups were carried out per protocol. No centralised assessment or independent clinical verification was reported for any of the outcomes.
Have the authors identified all important confoundin g factors?	Yes	All major influences on outcomes included: baseline characteristics and demographics (age at baseline, PDMS-2 baseline scores, AIMS baseline	Yes	Baseline characteristics of age and measurement scores relating to motor development are identified as potentially

		scores, Bayley-III baseline scores).		confounding. There are no time-varying confounding factors.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The primary analysis of efficacy does not involve any covariate adjustments. For the secondary endpoint analyses of PDMS-2, AIMS, and Bayley, repeated measures models included the covariates of baseline scores, age at the time of eladocagene exuparvovec infusion, and visit.	Yes	As per the company study assessment in the column to the left. No adjustments made for the primary efficacy endpoint Repeated measures models are appropriate.
Was the follow-up of patients complete?	Yes	9 of the 12 patients (75.0%) completed the follow-up at 12 months.	No	At the primary efficacy analysis timepoint (12 months) [redacted] (CSR Table 14.2.1.1.3) and data from [redacted] patients was included in the analyses in CS section B.2.6.2.1 and from [redacted] patients in the CSR.
How precise (for example, in terms of confidence interval and p-values) are the results?	Yes	95% confidence intervals used, and P-values provided for primary and secondary endpoints.	Yes	As per the company study assessment in the column to the left. 95% confidence intervals limited to the putaminal -specific uptake by PET imaging outcome only.

Source: partly reproduced from CS Table 107

Appendix 4

Table 58 List of additional NICE scope and decision problem related outcomes reported in the three pivotal eladocagene exuparvovec trials

Endpoint	Outcome type	Outcome measures
Secondary	Motor function	**Raw scores for the Alberta Infant Motor Scale (AIMS) total score/subscale** up to 12 months (AADC-011)/ 60 months (AADC-010, AADC-CU/1601)

		Raw scores for the AIMS subscales[a] up to 12 months (AADC-011)/ 60 months (AADC-010, AADC-CU/1601)
	Autonomic nervous system functioning	**Proportion with autonomic nervous system dysfunction symptoms**[b] up to 12 months (AADC-011, AADC-010, AADC-CU/1601)
	Cognitive, speech and language development	**Raw scores for the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) total score** up to 60 months (AADC-CU/1601 only)
		Raw scores for the CDIIT subscales[c] up to 60 months (AADC-CU/1601 only)
		Raw scores for the Bayley Scales of Infant Development – Third Edition (Bayley-III) total score[d] up to 12 months (AADC-011)/ 60 months (AADC-010)
		Raw scores for Bayley-III subscales scores[e] up to 12 months (AADC-011)/ 60 months (AADC-010)
	Changes in levels of neurotransmitter metabolites in the cerebral spinal fluid (CSF)	**Change from baseline in levels of neurotransmitter metabolites (homovanillic acid (HVA; the metabolite of dopamine) and 5-hydroxyindoleacetic acid (5-HIAA; the metabolite of serotonin) measured in the CSF** at 6 months / 12 months (AADC-011, AADC-010, AADC-CU/1601)
	Body weight	**Change from baseline in body weight (kg)** up to 12 months (AADC-010, AADC-011)/ 60 months (AADC-CU/1601); **Percentile of body weight shift from baseline** up to 12 months (AADC-010, AADC-011)

Sources: CS Tables 9, 10, and 11; Company clarification responses A17; AADC-010 CSR section 11.4.1.2.3; AADC-011 CSR section 11.4.2.3 and 11.4.2.4.

[a] Subscales included: supine, stand, sit and prone
[b] Symptoms were: ptosis, diaphoresis, temperature instability, nasal congestion, gastrointestinal dysmotility, and profuse secretion. Data were only collected for patients who experienced ANS symptoms at baseline (Company clarification response A17)
[c] Subscales included: social, self-help, motor total score, language, and cognition
[d] the sum of the cognitive, expressive communication, and receptive communication subscales scores only
[e] Subscales included: cognitive, expressive communication, and receptive communication

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 3 August 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Inclusion of Japanese studies in the appraisal

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 14-15, Table 1: "Uncertainty whether all relevant data have been included in the CS" On page 14-15, Table 1: "The EAG identified three studies of AAV-hAADC-2 administered into the putamen, conducted in Japan. It is unclear if the vector used in these studies was the same as the one used in the eladocagene exuparvovec studies. It is therefore unclear if this evidence should have been included in the CS." On page 14-15, Table 1: "If the studies conducted in Japan, identified by the EAG, used the same vector as in the eladocagene exuparvovec studies, the results should be summarised for consideration in this appraisal" The Company does not agree with this statement as the	The Company would like to request the removal of Issue 1 from the EAG report. Please see rows below for suggested amendments to text in other related areas of the report if the EAG accepts the request.	The Company would like to clarify that while the vector reported in Kojima (2019) is similar to eladocagene exuparvovec, is not the same. It is a proprietary vector for which details are not available to PTC. Patients reported in Kojima (2019) are therefore not relevant to this appraisal and the issue should be removed.	This is not a factual inaccuracy. We thank the company for confirming that the vector used in Kojima et al. (2019) was not the same as used in the eladocagene exuparvovec studies. The statements we made in our report, however, were not factually inaccurate and we have not removed Issue 1. The Evidence Assessment Group (EAG) notes in section 3.2.1.6 of our report that as the Kojima et al. (2019) publication states that a similar AADC-expressing AAV vector was used to that in the eladocagene exuparvovec studies, we assumed this was not the same as the one used in the eladocagene exuparvovec studies, but that this was not fully clear to us. We therefore decided to include

studies are not relevant to this appraisal.			this as an issue for consideration at the technical engagement stage of the appraisal, to fully ascertain that these data were not relevant. To better explain our meaning in key issue 1, we have now revised the description of the issue to read as follows: “The EAG identified three studies of AAV-hAADC-2 administered into the putamen, conducted in Japan. It was unclear to the EAG if the vector used in these studies was the same as the one used in the eladocagene exuparvovec studies; the studies’ publication describes the vector as similar to that used in the eladocagene exuparvovec studies. We assume this means it is not the same, but believe it would be useful to obtain confirmation that this evidence is not relevant to the appraisal.”

On Page 40: "A publication of the results related to these studies (Kojima et al., 2019)[11] states AAV-hAADC-2 is a similar AADC-expressing AAV vector to that used in the eladocagene exuparvovec studies. The EAG assumes that this means that it is not the same, but this is unclear. If it is the same vector, then results reported in this publication, which includes data for five people with the severe phenotype, may be relevant to this appraisal."	Replace text with: "A publication of the results related to these studies (Kojima et al., 2019)[11] states AAV-hAADC-2 is a similar AADC-expressing AAV vector to that used in the eladocagene exuparvovec studies. The EAG assumes that this means that it is not the same, which the Company has confirmed. As it is not the same vector, then results reported in this publication, which includes data for five people with the severe phenotype, are not relevant to this appraisal."	As above, the Company would like to clarify that the treatment reported in Kojima 2019 is a similar but not identical vector to eladocagene exuparvovec. The Company therefore requests an amendment to the wording to reflect that the Kojima 2019 patients are not relevant to the appraisal.	As stated above, this is not a factual inaccuracy. No change made.
On Page 81, bullet one: "The EAG identified three ongoing studies, conducted in Japan, with data published for participants with the severe phenotype who received AAV-hAADC-2 administered into the putamen.[11] It is unclear if this AADC-expressing AAV vector is the same as the one used in the eladocagene exuparvovec studies and	Replace text with: "The EAG identified three ongoing studies, conducted in Japan, with data published for participants with the severe phenotype who received AAV-hAADC-2 administered into the putamen.[11] The Company clarified that the AADC-expressing AAV vector is not the same as the one used in the eladocagene exuparvovec studies and therefore these data are not relevant to this appraisal."	As above, the Company would like to clarify that the treatment reported in Kojima 2019 is a similar but not identical vector to eladocagene exuparvovec. The Company therefore requests an amendment to the wording to reflect that the Kojima 2019 patients are not relevant to the appraisal.	As stated above, this is not a factual inaccuracy, no change made.

therefore whether these data are relevant to this appraisal."			

Issue 2 Discount rate

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 89: "While we view that eladocagene exuparvovec is targeted for patients with severely impaired life, it remains unclear: i) if the technology will restore patients to full or near-full health and ii) persistence of the benefits in the long term. Advice from our clinical expert suggests that eladocagene exuparvovec is unlikely to restore patients to full or near-full health as the gene-therapy is not curative. Secondly, while we acknowledge early indications of treatment benefits persisting based on the evidence of benefit up to 10 years in the study by Tai et al.[4] and data provided by the company in clarification	• The company propose the text on page 89 is replaced with: "While we view that eladocagene exuparvovec is targeted for patients with severely impaired life and who have missed key development steps by the time they are diagnosed and treated, it remains unclear if the technology: i) will restore patients to full or near-full health and ii) the benefits persist in the long term. Advice from our clinical expert suggests that there is uncertainty regarding persistence of treatment effect in the long-term due to lack of long-term follow-up. Secondly, while we acknowledge the strengths of 10 years of follow-up data and acknowledge that there is evidence of treatment benefits persisting up to 10 years based on data in the study by Tai et al.[4] and data provided by the company in clarification response A21, there is currently no data to support persistence of treatment benefit in the long-term beyond 10 years. Considering	The Company suggests the text is amended to acknowledge the strengths of 10 year of follow-up data for a new treatment for an ultra-rare disease and to reflect the clinical expert statements in the EAG report. The Company believes that eladocagene exuparvovec meets the criteria for the 1.5% discounting rate and that the 1.5% rate was intended to cover situations similar to this (that is, when costs are incurred upfront, but benefits are accrued over a longer period) to meet conditions stated for the non-reference 1.5% discount rate. Eladocagene exuparvovec corrects the underlying cause of AADC deficiency by replacing the non-functioning DDC gene.	We have noted the company's justification for their suggested amendment. However, this is not a factual inaccuracy. We have acknowledged the company's evidence of benefit up to 10 years (as reported in the study by Tai et al. and data provided by the company) in the EAG report. However, there remains uncertainty regarding the persistence of treatment benefit in the long-term beyond 10 years. On page 89, we have revised the text to include "…and who have missed key development steps by the time they are

response A21, there is currently no data to support persistence of treatment benefit in the long-term beyond 10 years. Considering the above uncertainties, we view that a discount rate of 3.5% is appropriate for both costs and effects in the current appraisal." Page 85, Table 23, "Discounting" row states: **"**A discount rate of 1.5% was applied for both costs and health effects in the base case. We disagree with the company's approach. (See Section **Error! Reference source not found.**)**"** Page 140 states: "The EAG considers that a discount rate of 3.5% is more appropriate since it is unclear (i) if the technology will restore patients to full or near-full health and (ii) whether the benefits will persist in the long-term. However, as uncertainties remain, we	the above uncertainties, we view that a discount rate of 3.5% is appropriate for both costs and effects in the current appraisal." • The company propose the text on page 85, Table 23, "Discounting" row is replaced with: "A discount rate of 1.5% was applied for both costs and health effects in the base case. Due to some uncertainties, we have instead applied a discount rate of 3.5% in our approach. (See Section **Error! Reference source not found.**)" • The Company propose the text on page 140 is replaced with: "The EAG considers that a discount rate of 3.5% is more appropriate since it is unclear (i) if the technology will restore patients to full or near-full health and (ii) whether the benefits will persist in the long-term. However, as we acknowledge the strengths of 10 years of follow-up data and acknowledge that there is evidence of treatment benefits persisting up to 10 years, uncertainties remain. Hence, we presented the results of the EAG analyses for the discount rates of 0%, 1.5% and	As stated in Company Response B6, AADC enzyme activity is sustained at 5 years follow-up. It also provides sustained clinical benefits up to 10 years, as noted in Company response A21. The treatment effect is expected to persist in the long-term, as noted in the EAG's clinical expert comments in the EAG report: "Clinical advice to the EAG is that, due eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time." (Page 67 of EAG report). Furthermore, as highlighted by the EMA, rAAV2 was chosen as the vector for delivery due to its demonstrated long-term gene expression in the CNS. The Company would also like to note that the "full health" criteria is ambiguous and may not be possible for a disease like AADC deficiency as AADC deficiency begins from birth and affected patients suffer from loss of key developmental milestones	diagnosed and treated". We have made no further change to text. Page 85, Table 23: Not a factual inaccuracy. Therefore, no change to text. Page 140: Not a factual inaccuracy. Therefore, no change to text.

presented the results of the EAG analyses for the discount rates of 0%, 1.5% and 3.5% to illustrate the impact of this assumption on the overall cost-effectiveness results.”	3.5% to illustrate the impact of this assumption on the overall cost-effectiveness results.”	before they are diagnosed and treated. Despite this, some patients with AADC deficiency are able to walk and talk within years of treatment with eladocagene exuparvovec, and the timeframe of improvement in their development from the time of gene therapy is similar to that of a normal child from birth. This may be considered near full-health. The Company would also like to note that 10 years of follow-up data is rare for a therapy at the time of regulatory approval. Other therapies have had a 1.5% discount rate accepted based on less than 10 years of follow-up data, including TA538 (dinutuximab beta for treating neuroblastoma)[5] and TA235 (mifamurtide for the treatment of osteosarcoma)[6]. Furthermore, the Company considers the appraisal to be similar to HST 15 (onasemnogene abeparvovec for treating spinal muscular atrophy), which had a 1.5% discount applied to costs and	

		effects. In this appraisal, the committee “acknowledged that onasemnogene abeparvovec has a high one-off cost, whereas the benefits are accrued over the lifetime of the patient”. The committee also considered that “it was likely that the alternative 1.5% discounting rate was intended to cover situations similar to this (that is, when costs are incurred upfront, but benefits are accrued over a longer period)” and “acknowledged that the technology was transformative for people who, without treatment, would otherwise die.”. Additionally, the committee “was uncertain about whether most people who have onasemnogene abeparvovec would be considered to have ‘normal or near-normal health’ but believed a proportion might.”. These considerations are all relevant to eladocagene exuparvovec for treating AADC deficiency. The Company would also like to note that the UK Treasury Green Book states that “a reduced rate	

		of 1.5% per annum applies to policies that impact health or life outcomes".[7]	

Issue 3 Baseline severity and PDMS-2 score

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 36, Section 3.2.1.2: "The CS Executive Summary confirms that 28 participants had a diagnosis of severe AADC deficiency. It is unclear if the other two enrolled participants also had the severe phenotype. The participant eligibility criteria for the trials provided in CS Tables 9 to 12 do not appear to list a requirement for participants to have a severe phenotype"	Replace text with: "The CS Executive Summary confirms that 28 participants with a diagnosis of severe AADC deficiency were considered in the economic model. The other two enrolled participants also had the severe phenotype but did not have sufficient follow-up data due to the impact of COVID on follow-up assessments. While the participant eligibility criteria for the trials provided in CS Tables 9 to 12 do not appear to list a requirement for participants to have a severe phenotype, all participants in the studies had no key motor development milestone achievement at baseline (CS Table 14, Table 20, Table 25, and SmPC) including the ability to sit, stand or walk, compatible with the severe phenotype."	Provides further clarity on the statement. As stated in the SmPC, all participants in the eladocagene exuparvovec studies had not achieved motor development milestones at baseline including the ability to sit, stand or walk, compatible with the severe phenotype.	This is not an EAG factual inaccuracy, no change made. We have reviewed the draft Summary of Product Characteristics (SmPC) and the final SmPC (which is now available on the European Medicines Agency website) and neither state that *all* participants had no motor function. We note that the SmPCs state that studies AADC-010 and AADC-011 included 20 participants with severe AADC deficiency. As is shown in Table 7 of our report, 22 participants were enrolled into these two studies, which leaves two

			participants unaccounted for. We thank the company for clarifying now (i.e. at this factual accuracy check stage of the appraisal) that all participants had the severe phenotype and for making it clear here that the two unaccounted for participants were the two in study AADC-011 who were lost to follow-up due to the impact of COVID-19. Regarding the company's suggested wording about how no motor function is compatible with the severe phenotype, we have already explained in section 3.2.1.2 of our report that participants had no motor function at baseline and that this is reflective of the company's definition of the severe phenotype; a definition which our clinical expert agreed was reasonable.
Page 41, 1st paragraph:	Replace statement:	Provides further clarity on outlier and the comparison of baseline	This is not a factual inaccuracy, but we agree to amend the statement to

"Patients in the AADC-011 trial appear to have a higher PDMS-2 score for motor function although it looks like this may be due to an outlier because although the maximum score is high the median score is similar."	"Patients in the AADC-011 trial appear to have a higher baseline mean PDMS-2 score for motor function than the other studies, although it looks like this may be due to an outlier because although the maximum score is high the median score is similar for AADC-010, AADC-011, and AADC-CU/1601 ([redacted], [redacted] and [redacted], respectively)."	PDMS-2 total scores across the trials.	make the comparison clearer. We have now altered the statement to read as follows: "Patients in the AADC-011 trial appear to have a higher mean PDMS-2 score for motor function than participants in the other two studies, although it looks like this may be due to an outlier because although the maximum score is high the median score ([redacted]) is similar to that in the AADC-010 study ([redacted]) (median score not reported for the AADC-CU/1601 study)."

Issue 4 Use of PDMS-2 in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93 states: "Consultation with our clinical expert suggested that assessment of motor milestones in a busy NHS clinic is not usually based on formal motor scales, except perhaps GMFCS grades/categories. We	The Company propose the wording is amended to: "Consultation with our clinical expert suggested that assessment of motor milestones in a busy NHS clinic is not usually based on formal motor scales, except perhaps GMFCS grades/categories. Instead, motor function	The Company would like to suggest wording changes to acknowledge the validity and appropriateness of the PDMS-2 scale for the eladocagene exuparvovec trials and the CS model.	We have noted the company's justification for amending our statement. However, this is not a factual inaccuracy. Our statement is based on our clinical expert opinion.

note the motor milestone achievement states seem to be more reflective of how motor function is assessed in practice than the PDMS-2 scores." The Company propose that the EAG consider the use of PDMS-2 scores as a valid method for measuring motor milestone achievement within patients with AADC deficiency.	is assessed by clinician judgement and may therefore vary from clinician to clinician and may not provide a complete picture of patient motor function. We note that CS Section B.3.2.2.7 states that PDMS-2 scoring provides a validated, specific, sensitive and reliable method for measuring motor milestone attainment and gives objective and granular data on motor function beyond just the key motor milestones."	PDMS-2 is appropriate as it is a validated, rigorous and reliable measure of motor function and has been used in AADC deficiency in a natural history study of 37 patients in Taiwan (as noted in CS Section B.3.2.2.7).[8] The 2017 international consensus clinical guidelines for AADC deficiency, which are followed in UK practice (as noted in EAG report Section 2.2.1.5)[1], do not mention a preferred measure for assessing motor function in AADC deficiency, suggesting that there is no single widely recognized and accepted measure in AADC deficiency. Natural history data in AADC deficiency do not exist using motor function instruments other than PDMS-2. The Company believes that the PDMS-2 scale gives a more reliable and sensitive measure of motor function than "clinician judgement", which is more subjective. In a 2018 comparison of instruments to measure child gross motor function, PDMS-2 was noted as	Therefore, no change to text.

		having excellent test-retest reliability and was stated as being among the most reliable assessments for gross motor function in children.[9] The 2018 comparison also states that PDMS-2 is the only measure that is sensitive to partial mastery of a task and one of only four tools with a reported minimum clinically important difference (MCID) with satisfactory sensitivity and specificity.[9] This is particularly pertinent as EAG report Section 3.2.3.1 states that "our expert also thought it reasonable and clinically relevant to consider both 'newly emerging' skills and 'mastery' of key motor milestones." In addition, as noted in CS Section B.3.2.2.7, the use of PDMS-2 was accepted by NICE as an appropriate instrument to measure motor function in studies that informed the NICE clinical guideline on the diagnosis and management of CP, and was shown to have good test-retest reliability,	

		responsiveness, and sensitivity to change in a study exploring its validity in CP.[10,11] It has been used in CP, autism, Down syndrome, Hurler syndrome, and to explore the effects of biological (e.g. prematurity, malnutrition) and environmental (e.g. socioeconomic status, family routine) variables on normal child development.[10] It has also been validated in various populations across various geographies[10], and considered a reliable tool used in several countries.[12] Therefore, the Company considers the use of PDMS-2 scores as rigorous, reliable, granular, and appropriate for measuring motor function and key motor milestone achievement in the eladocagene exuparvovec clinical studies and in the CS economic model. The appropriateness of PDMS-2 scores as a measure for motor milestone achievement further supports the proposed	

		amendment highlighted in Issue 5.	
Page 47 states: "PDMS-2 total score (the EAG believe this outcome was used to predict motor milestone achievement in the company's base case)."	Replace statement with: "PDMS-2 total score (this outcome was used to predict motor milestone achievement in the company's base case)."	Provides clarity on company base methodology for predicting motor milestone attainment. As previously mentioned in this table, the Company strongly believes that the method of using PDMS-2 total score to predict motor milestone achievement is robust, realistic, and makes the most of the available data regarding patient motor function.	This is not a factual inaccuracy and we have therefore not amended the report. We chose to use the word "believe" here, as whilst it appeared from the company submission that this outcome was used to predict motor milestone achievement in the company's base case, the company's response to clarification question A9 stated, "It should also be noted that PDMS-2 total score was not used in the economic model. The economic model uses the key motor milestone attainment, which was measured in the eladocagene exuparvovec trials." Thus we felt there was a lack of clarity about whether or not the total score was used.
Page 68 states:	The Company suggests that the text is removed, as the Company can confirm	Clarifies the use of AADC-011 data in the model.	We thank the company for clarifying this, but this is

"It is also unclear if the additional long-term follow-up data from study AADC-011 beyond 12 months was incorporated into the model."	that AADC-011 data beyond 12 months were incorporated into the model.		not a factual inaccuracy, as this information was not available to the EAG at the time we wrote our report. No change made.

Issue 5 Motor milestone achievement in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Page 93 states: "Comparing the company's predicted distribution of patients across the motor milestone health states (based on PDMS-2 scores) with the observed distribution from the trials naïve analysis with LOCF, we observe that the predicted estimates in the 'worst' health state - 'no motor function' - is lower compared to the observed value (presented in **Error! Reference source not found.** and **Error! Reference source not found.** below). Whereas for the remaining health states, the predicted estimates are, in general, higher than in the observed	• The Company proposes the wording on Page 93 is amended to: "Comparing the company's predicted distribution of patients across the motor milestone health states (based on PDMS-2 scores) with the observed distribution from the trials naïve analysis with LOCF, we observe that the predicted estimates in the 'worst' health state – 'no motor function' – appear lower than the observed value (presented in **Error! Reference source not found.** and **Error! Reference source not found.** below). For the remaining health states, the predicted estimates are, in general, higher than in the observed distribution. For the 'best' motor milestone state – 'walking with assistance' – the predicted estimates are significantly higher than the observed distribution.	The Company propose that the EAG consider the Company's predicted distribution approach as the base-case for the economic analysis. The Company would also like to point out that the observed and predicted distribution approaches are not directly comparable as the observed approach assumes no future motor milestone attainment beyond the last follow-up, whereas the predicted distribution approach allows motor milestones to be attained beyond the last follow-up visit. The LOCF method of predicting motor milestones biases against patients who were treated within	Not a factual inaccuracy. Therefore, no change to text on pages 93, 94 and 131 (Table 48). We have noted the company's arguments. However, our justification for choosing the observed distribution from the trials naïve analysis with LOCF are summarised in EAG report Section 4.2.6.1.1. To reiterate, the company's approach of using the Bayesian growth curve model is reasonable based on the assumption that there is no deterioration of motor

distribution. In particular, for the 'best' motor milestone state- 'walking with assistance' the predicted estimates are significantly higher than the observed distribution. This is an important issue as using the predicted motor milestone health states would potentially overestimate the effectiveness of eladocagene exuparvovec, favouring the intervention arm compared to best supportive care." • Page 94 states: "Considering the above uncertainties associated with using PDMS-2 scores as a predictor for motor milestone achievement, we view it as appropriate to use the observed patient distribution across the motor milestone health states from the three eladocagene exuparvovec studies as the base case for this appraisal." • Page 131, Table 48, "Motor Milestones – Eladocagene	It should be noted that the observed distribution approach carries the last observation forward and therefore assumes that patients cannot attain any motor milestones after their last follow-up visit. This may underestimate the effect of eladocagene exuparvovec as the clinical data show that some patients with limited follow-up data are on an upward trajectory in motor development (as evidenced by increasing PDMS-2 total scores) at the point of their last follow-up visit and may therefore attain motor milestones in the future. The Company's method of predicting motor milestone achievement allows for a patient with limited follow-up to continue their PDMS-2 trajectory to the end of the developmental phase in the model. This future projection of motor milestones with the predicted distribution approach and not the observed distribution approach is the reason that the predicted approach appears to estimate higher motor milestone attainment than the observed approach." • The Company propose the wording on page 94 is amended to: "Therefore, even considering the above uncertainties associated with using PDMS-2 total scores as a predictor for motor	the past 2-3 years and therefore have less follow-up data. Many patients with longer follow-up data continuously improve in motor milestone achievement up to and beyond 5 years post-gene therapy. For example, one patient with 6 years of follow-up data demonstrates continuous motor improvement over the course of these 6 years, achieving the following: [redacted]. The clinical data show that some patients with limited follow-up are on an upward trajectory in terms of PDMS-2 score and motor milestone attainment at the time of their last follow-up. It is reasonable, therefore, to assume that some patients would continue to improve in PDMS-2 scores and attain motor milestones in future (i.e. following their last follow-up), as is the case with the predicted distribution approach.	milestones. The company did not report the motor milestone trajectories of the 28 patients; therefore, we are unable to ascertain the validity of this assumption. Secondly, in company submission (CS) Figure 58 of Appendix J, there is at least one patient with a downward PDMS-2 trajectory which contradicts the company's asymptote assumption.

Exuparvovec" row, "ERG preferred" column states: "Modelling through observed trial distribution, using LOCF for missing data imputation"	milestones achievement, the EAG consider the Company's preferred method of a predicted distribution of motor milestones through growth models as a reasonable method for the cost-effectiveness base-case." • Page 131, Table 48, "Motor Milestones – Eladocagene Exuparvovec" row, "ERG preferred" column: The Company requests that the EAG reviews and reconsiders their preferred approach based on the information provided in this Issue.	Assuming that a patient would not gain any motor milestones in the future makes the observed distribution approach inappropriate for the base case. The observed distribution with LOCF approach should therefore be used as a scenario analysis as it is limited by a lack of follow-up data for some patients and implausibly assumes that patients gain no additional motor milestone attainment beyond their trial follow-up. Given that some patients have only 12 months of follow-up in the model, yet most patients accrue motor milestones for at least 5 years, the last observation carried forward approach for the observed distributions is unrealistic and biases the results against eladocagene exuparvovec. The Bayesian modelling approach proposed by the Company uses the modelling of PDMS-2 as a proxy to estimate the likelihood of a patient being in each motor milestones over time. For patients with limited	

		follow-up, it continues their PDMS-2 trajectory to the end of the developmental phase and therefore allows patients to attain motor milestones beyond their last follow-up visit. The EAG considered the length of 12 years for the developmental phase a “reasonable assumption based on clinical evidence” as “the development duration is consistent with that of a development of a healthy child”. The fitted growth curves are all shown to fit the observed data well, with the preference of the Gompertz model as the base-case curved based on internal validation (see Figure 63 and Figure 64 of the CS). The asymptotic curve was used as a scenario analysis and presented to the EAG. The second stage of the predicted distribution approach takes into account that a patient with a given level of motor skill (i.e. PDMS-2 score) is associated with a particular motor milestone. This implies that as a patients PDMS-2 score increases they are more likely to	

		have gained a higher motor milestone.	
Page 121 states: **“**The internal validation of the cumulative ordered logit model against the observed PDMS-2 scores show that the model predictions are more optimistic than the observed values and hence benefit eladocagene exuparvovec, since they predict fewer patients in the severe health states and more patients in the better (less severe) health states.”	The Company propose the wording on page 121 is amended to: “The internal validation of the cumulative ordered logit model against the observed PDMS-2 scores shows that the model predictions are higher than the observed values. However, it should be noted that the observed distribution approach and the predicted distribution approach differ in their approach to modelling motor milestone attainment beyond the trial follow-up. The observed data approach uses LOCF from each patient’s last follow-up visit and therefore assumes that patients cannot attain any motor milestones after their last follow-up visit. This is likely to underestimate the effect of eladocagene exuparvovec as the clinical data show that some patients with limited follow-up data are on an upward trajectory in motor development (as evidenced by increasing PDMS-2 total scores) at the point of their last follow-up visit and may therefore attain motor milestones in the future. The Company’s predicted distribution approach models motor milestone	The Company do not think it is accurate to say that the cumulative ordered logit models predictions are more “optimistic” than the observed values. As demonstrated in the above row in this table, the observed and predicted distribution approaches are not directly comparable as the observed approach assumes no future motor milestone attainment beyond the last trial follow-up visit, whereas the predicted distribution approach allows motor milestones to be attained beyond the last follow-up visit. The Company strongly believes that the predicted distribution approach is more robust and reflective of the true effect of eladocagene exuparvovec, based on the clinical data, it is unreasonable to assume that patients who are improving in PDMS-2 scores at their last follow-up visit would not attain any new key motor milestones	We have noted the company’s arguments. However, this is not a factual inaccuracy. Hence, no change to text. While we acknowledge the company’s statement that some patients with limited follow-up data are on an upward trajectory in motor development (as evidenced by increasing PDMS-2 total scores) at the point of their last follow-up visit and may therefore attain motor milestones in the future, we also note that there is at least one patient with a downward PDMS-2 trajectory which contradicts the company’s assumption (as shown in CS Figure 58 of Appendix J). Our conclusion in Page 121 is based on our internal validation as part

	attainment beyond each patient's last follow-up visit based on their PDMS-2 scores and therefore allows for potential future motor milestone attainment beyond the trial follow-up, analogous to development spanning several years during childhood."	in future as they continue to grow and develop (analogous to development during childhood in a healthy individual). See the above point in this table for a detailed justification.	of which we compared the patient distribution across the motor milestone health states as estimated by the company's base case approach (using PDMS-2 scores) and using observed values based on naïve analysis using LOCF approach, shown in Figure 4, Page 95 of the EAG report.
Page 123 states: "The EAG notes that the company's estimates are more optimistic than those observed in the trials, with more patients achieving better health states (such as standing with support and walking with assistance) and fewer remaining with no motor function."	The Company propose the wording on page 123 is amended to: "The EAG notes that the company's estimates are higher than those observed in the trials, with more patients achieving better health states (such as standing with support and walking with assistance) and fewer remaining with no motor function. However, the Company's predicted distribution approach models motor milestone attainment beyond each patient's last follow-up visit based on their PDMS-2 scores and therefore allows for potential future motor milestone attainment beyond the trial follow-up, whereas the observed data approach does not."	The Company do not think it is accurate to say that the cumulative ordered logit models predictions are more "optimistic" than the observed values, as described in the rows above. The Company would therefore like to request that this is updated to explain the differences of the approaches and recognise that the two methods are not directly comparable and interchangeable	Not a factual inaccuracy. Hence, no change to text. Please refer to our above comments.

Page 140 states: "The EAG have concerns about the company's approach of using PDMS-2 scores to predict motor milestone achievement (see section **Error! Reference source not found.** for further details on the company's methods) rather than using the data observed directly in the trials due to the following reasons: i) motor milestone achievement is more reflective of how motor function is assessed in NHS practice than the PDMS-2 scores; ii) the prediction of motor milestone achievement through PDMS-2 scores overestimates the effectiveness of eladocagene exuparvovec compared with estimates from observed data (see section **Error! Reference source not found.** and **Error! Reference source not found.** above); and, iii) this approach lacks consistency with the approach adopted for the best supportive care arm where the observed values obtained from the company's naïve analysis	The Company propose the text on page 140 is amended to: "The EAG have concerns about the company's approach of using PDMS-2 scores to predict motor milestone achievement (see section **Error! Reference source not found.** for further details on the company's methods) rather than using the data observed directly in the trials due to the following reasons: i) motor milestone achievement is more reflective of how motor function is assessed in NHS practice than the PDMS-2 scores (though it is acknowledged that PDMS-2 is validated, rigorous and granular); ii) the prediction of motor milestone achievement through PDMS-2 scores does not align with estimates from observed data (see section **Error! Reference source not found.** and **Error! Reference source not found.** above); and, iii) this approach lacks consistency with the approach adopted for the best supportive care arm where the observed values obtained from the company's naïve analysis are used. Therefore, there are uncertainties as to the appropriate approach to modelling motor milestone achievement in the base case."	The Company disagree with the statement that "the prediction of motor milestone achievement through PDMS-2 scores overestimates the effectiveness of eladocagene exuparvovec compared with estimates from observed data". As previously discussed in the above row in this table, the observed and predicted distribution approaches are not directly comparable as the observed approach assumes no future motor milestone attainment beyond the last trial follow-up visit, whereas the predicted distribution approach allows motor milestones to be attained beyond the last follow-up visit.	We have noted the company's disagreement with the EAG's view. However, this is not a factual inaccuracy, as explained in our comments in the above rows. Hence, no change to text.

are used. Therefore, we use the observed data on motor milestone achievement from the eladocagene exuparvovec clinical trials in our preferred base case."			
On Page 37: "In the base case, participants' motor milestone development was predicted using a Bayesian growth model, rather than using motor milestones achievement results directly observed in the trials (CS section B.3.3)."	Amend statement to: "In the Company base case, participants' motor milestone development was predicted based on observed PDMS-2 total scores using a Bayesian growth and cumulative ordered logit model, rather than using motor milestones achievement results directly observed in the trials (CS section B.3.3). This was to model future motor milestone attainment in those patients with limited follow-up data in the clinical trials."	Provides clarity and rationale for the Company's base case modelling approach. As noted in the above rows, the Company strongly believes that the method of using PDMS-2 total score to predict motor milestone achievement is robust, realistic, and makes the most of the available data regarding patient motor function.	This is not a factual inaccuracy. Nonetheless, we have included the word '…company's base case…' for clarity. We do not view it necessary to provide the company's rationale for their base case assumption at this point in the EAG report as we clearly stated that we critique their approach in Section 4.2.6 of the EAG report in the following sentence of the report.

Issue 6 Motor milestone achievement results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 124-126, Table 41:	The company propose that the row label for: "Company's scenario using observed trial data[c]"	Table 41 presents three sets of data for the proportion of patients achieving each motor milestone; Observed trial data	Not a factual inaccuracy. Nonetheless, we have

Row label: “Company’s scenario using observed trial data[c]” Footnote c: “Modelled estimates using the observed trial data on the achievement of motor milestones (based on the LOCF approach to impute missing values)”	is amended to: “Company’s scenario using observed trial data (LOCF approach)[c]”. The company propose that text in footnote ‘c’ is amended to: "Modelled estimates using the observed trial data on the achievement of motor milestones (based on the LOCF approach to impute missing values; last observation defined as the last follow-up visit for each patient) with background mortality and the half-cycle correction applied”.	(LOCF approach), Company’s revised base case, Company’s scenario using observed trial data. The Company would like to clarify that differences in motor milestone attainment percentages in the “Observed trial data (LOCF approach)” and “Company’s scenario using observed trial data” is due to the Company’s scenario including background mortality and a half-cycle correction. The Company confirms that the clinical trial data approach are the same in both approaches, as is the LOCF approach. The suggested edits are therefore to clarify that the differences in the two scenarios is due to the mortality and half-cycle correction.	revised the text in Table 41 and Page 123 for clarity.
Page 123 states: “For clarity and completeness, we also provide the estimates obtained from the scenario using the motor milestone achievement measured	Amend text to: “For clarity and completeness, we also provide the values obtained from the scenario using the motor milestone achievement measured directly in the eladocagene exuparvovec clinical trials (based on the LOCF approach to impute	As clarified in the row above, the suggested edits are to clarify that the differences in the two scenarios is due to the mortality and half-cycle correction.	

directly in the eladocagene exuparvovec trials”	missing values; last observation defined as the last follow-up visit for each patient) with background mortality and the half-cycle correction applied”		

Issue 7 AADC-011 longer-term follow-up data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 60, final paragraph: “AADC-011: [redacted] patients had follow up > 12 months (30 months, n=[redacted]; 48 months, n=[redacted]; 60 months, n=[redacted]; information not reported for [redacted] patient). Compared to 12 months post-surgery, [redacted] patients improved their motor milestone attainment and [redacted] maintained their motor milestone attainment.”	Replace wording with: “AADC-011: At the time of the latest data cut (data on file), [redacted] patients had follow up > 12 months. [redacted] had 24 months of data, [redacted] had 36 months of data, [redacted] had 48 months of data, [redacted] had 54 months of data, and [redacted] had 60 months of data. Compared to 12 months post-surgery, [redacted] of [redacted] patients with follow-up beyond 12 months improved their motor milestone attainment and [redacted] of [redacted] maintained their motor milestone attainment.”	Provides clarity on longer-term follow up data for AADC-011. Values were reported erroneously in Company clarification response A21 due to a typographical error.	This is not a factual inaccuracy on the part of the EAG; we correctly reported the values stated in the company’s clarification response. However, to sign-post the reader to the corrected values, we have added the following text to the bullet point reporting the long-term results from AADC-011 in section 3.2.5.1: “Please note that at the factual accuracy check stage of the appraisal, the company identified that the numbers of participants stated to have been followed up at each timepoint were reported

			erroneously in clarification response A21. The company clarifies the numbers followed up at each timepoint in factual accuracy check Issue 7. This does not affect the total number of participants followed up (n = [redacted]) nor the results reported above, which remain the same."
On Page 67, final bullet: "However, it is not clear to the EAG whether the LOCF approach was used to estimate motor milestone achievement for the participants in study AADC-011 beyond 12 months. Clarification response B18 states the approach was used to estimate outcomes for participants with less than five years data; this may mean it was used for the participants in AADC-011, but this is not clear. It is also unclear if the additional long-term follow-up data from study AADC-011	Replace wording with: "Long-term follow-up data beyond 12 months from the AADC-011 study were incorporated into the model, including in the observed data motor milestone scenario with the LOCF approach."	Clarifies that long-term follow-up data were included in the model and in the motor milestone achievement values using the LOCF approach. It should be noted that the economic model uses a February 2020 data cut. Furthermore, the Company does not believe that the LOCF approach "estimates" motor milestone achievement is appropriate. The LOCF approach uses observed trial data and assumes no future motor milestone achievement beyond the last follow-up. This is discussed further in Issue 5.	We thank the company for clarifying that the long-term follow-up data were included in the model, but the EAG's original statement is not a factual inaccuracy, as this information was not available to the EAG at the time we wrote our report. No change made.

beyond 12 months was incorporated into the model."			
On page 82: "It is unclear if the long-term follow-up motor milestones achievement results collected between >12 months and five years post-surgery in study AADC-011 have been used in the company's economic model scenario analysis, which uses the motor milestone achievement results directly from the studies."	Replace wording with: "In the company's economic model scenario analysis that uses the motor milestone achievement results directly from the studies, follow-up data from beyond 12 months in AADC-011 were included."	Clarifies that the model does include data from over 12 months of follow-up. It should be noted that the economic model uses a February 2020 data cut.	As stated above, we thank the company for clarifying this, but this is not a factual inaccuracy, as this information was not available to the EAG at the time we wrote our report. No change made.

Issue 8 Sample size calculation in the clinical studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54, 1st paragraph: "The EAG did not identify any issues with the statistical methods used in the three pivotal eladocagene exuparvovec studies, except for two issues. First, a lack of clarity around sample size calculation for studies AADC-	Replace wording with: "The EAG did not identify any issues with the statistical methods used in the three pivotal eladocagene exuparvovec studies, except for two issues. First, the EAG recognize that there was not a formal sample size calculation in all three studies as the studies were undertaken in an ultra-	Provides clarity on sample size calculations in AADC-010 and AADC-CU/1601. In all three studies, there was no formal sample size calculation due to the very limited patient numbers, which is to be expected given the	As stated in our report in Table 14, page 52, we acknowledge that the clinical study reports (CSRs) report that [redacted]. However, as is also stated in Table 14, CS Table 13

CU/1601 and AADC-010, which means it is uncertain whether these two studies were sufficiently powered to detect statistically significant results.”	rare disease with very limited patient numbers.”	ultra-rare nature of AADC deficiency.	reports the statistical power for studies AADC-CU/1601 and AADC-010, but it is unclear if the power was calculated *a-prior* or post-hoc. Therefore, in our opinion, there was a lack of clarity from the information we had available to us at the time we wrote our report around the sample size and power calculations. Rather than using the wording suggested by the company to amend the text on page 54, we have now altered it to make it clear that the statement about the lack of clarity around the sample size calculations is the EAG’s opinion, as follows: “First, in the EAG’s opinion, there is a lack of clarity around sample size calculation for studies AADC-CU/1601 and AADC-010…”.
Page 52, Table 14, 2nd, section: “There was no formal sample size calculation (AADC-	Replace text in Page 52, Table 14, 2nd, section with: “There was no formal sample size calculation (AADC-CU/1601, AADC-010,	Provides clarity on sample size calculation. In all three studies, there was no formal sample size	None of the EAG’s statements about the sample size calculations in Table 14 on page 52 are

CU/1601, AADC-010, AADC-011 CSRs sections 9.7.4).” Page 52, Table 14, 2nd section “It is unclear whether a formal sample size was calculated for studies AADC-CU/1601 and AADC-010. It is uncertain whether these two studies were sufficiently powered to detect statistically significant results.”	AADC-011 CSRs sections 9.7.4) as the studies were conducted in an ultra-rare disease with very limited patient numbers.” Replace text in Page 52, Table 14, 2nd section with: “No formal sample size was calculated for all studies as the studies were conducted in an ultra-rare disease with very limited patient numbers.”	calculation due to the very limited patient numbers, which is to be expected given the ultra-rare nature of AADC deficiency.	factually inaccurate. We have, however, revised our ‘EAG comment’ section in the table to make the reasons for our summarising comment clearer and to make it clearer that the comment is the EAG’s opinion. We have amended the text to read as follows: “Due to the apparently conflicting information in the CSRs and CS Table 13, it is unclear to the EAG whether a formal sample size was calculated for studies AADC-CU/1601 and AADC-010. The EAG also believes it is uncertain whether these two studies were sufficiently powered to detect statistically significant results.”

Issue 9 Total number of trial patients included in the appraisal

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 37: “The company’s economic model base case uses data from 28 of the participants. It	Replace text with: “The company’s economic model base case uses data from 28 of the participants. Data from the other two enrolled	Improves factual accuracy of statement.	We do not consider this to be a factual inaccuracy. The EAG believes that the CS does not explicitly state

is unclear to the EAG why data from the other two enrolled participants were not used."	participants (Subjects [redacted] and [redacted]) were not used due to COVID-19 travel restrictions preventing follow-up after Month 6, leading to insufficient data being recorded. This point was clarified in CS section B.2.6.2.2. ("Not all subjects were able to return for follow-up visits, primarily due to the COVID-19 pandemic").		the reason why data from two of the 30 enrolled participants were not included in the economic model. We have acknowledged in our report in Table 8, section 3.2.1.5, that CS section B.2.3.1.3 states that in study AADC-011 two participants were unable to attend the 12-month follow-up due to the COVID-19 pandemic. It is unclear to the EAG from the CS if these were the two participants who were not included in the model. We have checked the text in CS section B.2.6.2.2, to which the company sign-posts here, and this section does not explicitly state that the participants who did not return for follow-up visits due to the COVID-19 pandemic were the two participants who were not included in the model. We have therefore not amended the text in our report.

On page 42, final paragraph: "By the EAG's calculations, two enrolled participants have not been included in the results presented in the CS and the reasons for this are unclear."	Replace statement with: "Two enrolled participants could not attend follow-up visits due to COVID-19 travel restrictions, so their results were not included in the CS. This point was clarified in CS section B.2.6.2.2. ("Not all subjects were able to return for follow-up visits, primarily due to the COVID-19 pandemic").	Provides further clarity as to why there is a discrepancy in the CS between the baseline population (N=12) and the population used for the results (N=10) for AADC-011.	We have now entirely removed the following text from the 'EAG comment on included studies' section (the final paragraph referred to by the company, which falls at the very end of section 3.2.1), as, despite the discrepancies in the numbers of participants reported to have been followed up in parts of the CS, clarification response and CSRs, the EAG was in the end able to account for all the participants (as already described in section 3.2.1.5): "There are some discrepancies between parts of the CS, clarification response and CSRs about the numbers of participants followed up at the '12 month' timepoint in study AADC-011 and the '60 month' timepoint in AADC-CU/1601. By the EAG's calculations, two enrolled participants have not been included in the results presented in the CS and the reasons for this are

			unclear." We have removed this from the 'EAG comment…' section as it was at odds with our earlier statements.
Page 68, 3rd paragraph: "The EAG notes that only 28 of the 30 participants enrolled in the eladocagene exuparvovec studies are included in the pooled analysis in the CS Table 30 rather than all 30 participants. The EAG suggests that this is due to two participants in study AADC-011 being lost to follow-up as they could not attend the 12-month visit. However, the reason for why only 28 participants are included is not explained in the CS. It is unclear to the EAG why the other two participants could not be additionally included in the pooled estimate, with their missing data estimated through the LOCF approach (i.e. carrying their motor milestone values from	Replaced statements with: "The EAG notes that only 28 of the 30 participants enrolled in the eladocagene exuparvovec studies are included in the pooled analysis in the CS Table 30 rather than all 30 participants. The EAG understands that this is due to two participants in study AADC-011 being lost to follow-up as they could not attend the 12-month visit due to COVID-19 travel restrictions (CS section B.2.6.2.2). It is unclear to the EAG why the other two participants could not be additionally included in the pooled estimate, with their missing data estimated through the LOCF approach (i.e. carrying their motor milestone values from baseline forwards). The LOCF approach would be a conservative analysis and would likely lead to bias against eladocagene exuparvovec given that most patients have been shown improvements in motor function and achieve motor milestones following treatment."	Provides further clarity as to why there is a discrepancy in the CS between the pooled ITT population (N=30) and the pooled population used for the primary endpoint analysis (N=28). As stated in Issue 5, the company would like to reiterate that the LOCF approach is not appropriate for the pooled analysis or economic model as it does not allow for potential future improvement in motor milestones for those patients with shorter follow-up in the trials. This unfairly biases the data against eladocagene exuparvovec and does not align with the clinical data, which shows that most patients continue to accrue motor milestones until at least 5 years post-gene therapy and that those patients with shorter follow-up are on an upward	This is not a factual inaccuracy, no change made. We thank the company for clarifying that the two participants not included in the pooled analysis were indeed the two participants lost to follow-up in study AADC-011, as the EAG assumed was probably the case (NB. we had already stated this assumption in the text to which the company refers). However, the EAG believes that the CS did not explicitly state that these participants were the two missing from the pooled analysis.

baseline forwards). This would be a conservative analysis."		trajectory in their PDMS-2 scores. The Company strongly believes that the approach to predict future motor milestone attainment (based on PDMS-2 total score through Bayesian and cumulative ordered logit modelling) is more appropriate and realistic as it makes the most of the available data, captures improvements in motor function in between the key motor milestones, and allows for future motor milestones to be attained.	
On page 82, 4th bullet: "It is not clear why data from 28 of the 30 enrolled participants are used in the pooled analysis of the three eladocagene exuparvovec studies rather than all 30 participants, in CS Table 30 (i.e. the data that informs the company's scenario analysis). The EAG assumes that this is due to two participants in study AADC-011 being lost to follow-up due to not being	Replace text with: "Data from 28 of the 30 enrolled participants were used in the pooled analysis of the three eladocagene exuparvovec studies rather than all 30 participants, in CS Table 30 (i.e. the data that informs the company's scenario analysis). The EAG recognises that this is due to two participants in study AADC-011 being lost to follow-up due to not being able to attend the 12-month visit because of COVID-19 travel restrictions (CS section B.2.6.2.2).	As above, provides clarity on why the pooled analysis explores N=28 patients rather than N=30, and clarifies why the LOCF approach may bias the results against eladocagene exuparvovec.	As stated above, this is not a factual inaccuracy, so we have not amended our report. As we also state above, it was not fully clear to the EAG at the time we wrote our report which participants were excluded from the pooled analysis.

able to attend the 12-month visit. It is unclear to the EAG why these participants could not be additionally included in the pooled estimate, with their missing data estimated through the LOCF approach (i.e. carrying their motor milestone values from baseline forwards), which would be a more conservative analysis “	It is unclear to the EAG why these participants could not be additionally included in the pooled estimate, with their missing data estimated through the LOCF approach (i.e. carrying their motor milestone values from baseline forwards). The LOCF approach would be a conservative analysis but would likely lead to bias against eladocagene exuparvovec given that most patients continue to improve in motor function and achieve motor milestones over time following treatment.“		

Issue 10 Discrepancies in clinical data N numbers in Table 15 (Mastery)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 56, Table 15. The Company would like to clarify the correct numbers reported in Table 15.	For clarity, we recommend that Table 15 in the current version of the EAG report is replaced with **Error! Reference source not found.** in the Appendix of the EE FAC company response, as this resolves the	**Error! Reference source not found.** and the edits to the text provide extra clarity and evidence on the following points: • Clarity on the number of patients assessed at each timepoint. • Clarity on the relevant data to use for the number of patients	We have reviewed the company’s proposed amendments to Table 15 in the EAG report. We have determined that none of the corrections the company is proposing resulted from any associated errors the EAG made in our reporting.

	issues on the potential data discrepancies identified by the EAG. In summary, the discrepancies have arisen due to the following: (1) The motor milestone results are presented in CSRs in the following three different ways: Cumulative up to a visit (primary endpoint), Number observed at a visit, and new milestones achieved in between 2 visits. The primary endpoint is the cumulative number of subjects to have achieved a motor milestone up to a visit (as assessed by mastery of the PDMS-2 item) and therefore we believe it is most relevant to present these values in Table 15 and Table 16. (2) In the CS, the Company submitted a draft version of the final CSR for study AADC-011. Final tables and figures from the final CSR for AADC-011 were made available between the Company Submission and the EAG clarification questions, and the Company shared the files with the EAG at clarification questions. The discrepancy in the numbers is due to the use of draft vs final CSR data at CS vs EAG clarifications stage.	achieving each key motor milestone. The primary endpoint was measured as cumulative achievement of a motor milestone by that timepoint. As this is the primary endpoint, it is the most relevant data. • Correction of two rounding discrepancies where 1 decimal place was used instead of 2, in evidence for AADC-CU/1601 milestone achievement proportions. • Correction of one typographical error in the AADC-010 milestone achievement proportions. • Inclusion of data from the final tables and figures from the AADC-011 CSR. The final tables and figures were made available between the CS and EAG clarification stages. The evidence base increased from N=9 in the original CS to N=10 in **Error!**	The company's suggested corrections resolve discrepancies we identified between the CS and other data sources and errors in the company's reporting. We have reviewed CS Document B and cannot find any information detailing that the primary outcome was measured as cumulative achievement of a motor milestone at each timepoint. For example, CS Table 5 states that the primary outcomes in studies AADC-010 and AADC-CU/1601 were the proportions of participants achieving motor milestones at the 5 year/60-month timepoint, and that the primary outcome in study AADC-011 was the proportion of participants achieving motor milestones at the 1-year timepoint. We do not believe this information was provided

	Please see below and in red text in Table 1 in the Appendix of this document for the Company's proposed changes to Table 15 in the EAG report: • Changes to 'AADC-CU/1601 no. assessed' column: Selection of values from Table 2 in the Company EAG response A10, which is based on data on file generated to respond to question A10, as opposed to CS section B.2.6.3.2 values. These are the most appropriate values. • Changes to 'AADC-CU/1601 No. patients (%)' column: No changes. We accept the shift from 1 decimal place in the CS to 2 decimal places in the EAG report ([redacted] to [redacted]) for Month 12 sitting unassisted and Month 60 standing with support. • Changes to 'AADC-010 no. assessed' column: All values changed to match CSR table 14.2.1.3. Please note that the numbers reported in CS Table 14 were an error and should be removed. • Changes to 'AADC-010 No. patients (%)' column: The correct values to use are from Table 14.2.1.2 of the CSR. This table reports cumulative	**Reference source not found.** and in the EAG questions. Two patients were excluded as they could not attend follow-up due to COVID-19.	previously in CS Document B. The only motor milestone results labelled as 'cumulative' that are presented in CS Document B are in CS Figure 22 (NB these are 'emerging' and 'mastery' motor milestone results from study AADC-011, and not the primary outcome 'mastery' results). As the EAG believes that we have not made any errors in our reporting in our Table 15, we have not replaced it with the company's revised table. We have, however, noted in section 3.2.5.1 of our report the following (in response to this issue and also in response to factual accuracy check Issue 11 below): "Please note that at the factual accuracy check stage of the appraisal, the company provided revised versions of Table 15 and Table 16, which

	number of patients achieving mastery of a PDMS-2 item up to that timepoint, as per the primary endpoint of the study. The values reported in Table 14.2.1.3 are different and do not reflect the primary endpoint. • Changes to 'AADC-011 no. assessed' column: Month 12 values changed to align with final table 14.2.1.1.3 from AADC-011. Please note that the final tables and figures (which were provided to the EAG at clarification questions) has data for 10 patients, compared to 9 patients in the draft final CSR (included in the CS). Month 24 and 60 values are updated to align with data on file generated to respond to EAG clarification question A10 and A21. Please note that 1 patient from AADC-011 has 60 months of follow-up data, not 3 as reported in Company clarification A21. The Company apologises for this typographical error in the clarification questions. • Changes to 'AADC-011 No. patients (%)' column: Month 12 values aligned to AADC-011 CSR Table 14.2.1.1.3		included confirmation of which of the discrepant values were the correct ones to use (factual accuracy check Issues 10 and 11)." We have included this to sign-post the reader to these data for completeness.

On Page 55: "The EAG has noted that there are some discrepancies between the number of patients reported in the CS to be assessed (as outlined in section 3.2.1.5) or to have achieved a milestone compared to that reported in the relevant CSRs. The number and proportion achieving milestones in all three studies, and any discrepancies in numbers, are reported in **Error! Reference source not found.** and **Error! Reference source not found.** below."	Replace wording with: "The number and proportion achieving milestones in all three studies are reported in **Error! Reference source not found.** and **Error! Reference source not found.** below."	Based on Company clarification to Table 15 (described above), the Company believes there is no longer a discrepancy in the numbers.	This is not a factual inaccuracy. Please see our response in the row above – we have not replaced Table 15 with the company's revised table, as we do not believe that any of the corrections the company suggests above are the result of errors in our reporting. We have therefore not made the company's suggested change to the text.
On Page 55: "The EAG understands that the results in **Error! Reference source not found.** and **Error! Reference source not found.** show the number and proportion of participants among those who were assessed at each timepoint who showed achievement of a milestone at that point. The only exception to this, is for	Replace wording with: "The EAG understands that the 'No. patients (%)' results in Table 15 and Table 16 shows the cumulative number of participants who showed achievement of a milestone up to that timepoint, with the denominator value being the number of enrolled patients (except AADC-011, which used N=10 as 2 patients could not attend follow-up due to COVID-19 travel restrictions). The 'No. assessed' data show the number of patients	In line with the above, the Company proposes edits to clarify the values reported in the Tables	Please see our response in the two rows above. We have not replaced Table 15 with the company's suggested table. We do not believe the text on page 55 was incorrect. None of the tables in CS Document B presenting the data included in Table 15 stated that the results

the ‘emerging’ and ‘mastery’ results combined for study AADC-CU/1601 which show the cumulative number and proportion of participants who achieved each milestone up to the relevant timepoint over the course of the trials.”	who were assessed at that specific timepoint.”		were cumulative. Our understanding, as we stated, was that the results presented show the number and proportion of participants among those who were assessed at each timepoint who showed achievement of a milestone at that point.
On page 56: “Table 15: Key motor milestone achievement (mastery, i.e. score of 2 on relevant PDMS-2 item) by timepoint”	Amend wording to: “Table 15: Cumulative key motor milestone achievement (mastery, i.e. score of 2 on relevant PDMS-2 item) up to that timepoint”	As above, the Company would like to clarify that the primary endpoint was analysed as cumulative achievement by the timepoint.	This is not an EAG factual inaccuracy. In line with our response in the rows above, we have not amended the title of this table, as we have not replaced Table 15 with the company’s revised table. The title of Table 15 is in accordance with how the data were labelled in CS Document B.
On page 37, second paragraph: “The EAG found that the numbers of participants stated in the CS to have completed	Amend wording to: “The EAG noted that the numbers of participants to have completed the longest follow-up timepoint to be:	The Company would like to provide clarity on follow-up data information reported in the CS and Company clarification responses. Please see below for	We thank the company for confirming the numbers followed-up at each timepoint. The EAG correctly reported the numbers followed-up on

the longest follow-up timepoint in each study (60 months or more in AADC-010, up to 12 months in AADC-011 and up to 60 months in AADC-CU/1601) lacked clarity due to discrepancies in stated numbers between CS Tables 9 to 11, the clinical efficacy results presented in CS section B.2.6 and the company's clarification response (as shown in Table 8 and the accompanying footnotes below). The EAG therefore checked the numbers against the information available in the CSRs. Based on this check, it appears that the following numbers of participants had data available to inform the '60 month' results for studies AADC-010 and AADC-CU/1601 and '12 month' results for study AADC-011: • AADC-010: eight participants, with assessments for the '60 month' timepoint taking place between 48 to ≥ 60 months (assuming that 48 to < 60-month data was	• AADC-010 (60 months or more): N=8 for Month 60 (CS Table 14, CS Table 15). • AADC-011 (Up to 12 months): Previously N=9 for Month 12 (CS Table 19, CS Table 20), but updated to N=10 (Table 1) based on AADC-011 CSR update between CS and EAG clarification questions. • AADC-CU/1601 (Up to 60 months): N=7 at Month 60 (ERG clarification question A10, Table 2).	some extra detail on the rationale for the changes • The Company confirms that 8 patients had data at the 60-month timepoint in AADC-010. N=8 is therefore the appropriate number to use. • The AADC-011 CSR was a draft version at the time of drafting the CS, so data for N=9 patients were available. At EAG clarification questions, data from the final tables and figures from the AADC-011 CSR became available and included data for N=10 patients (NB. The final CSR document was not available at the time of providing responses to clarification questions). N=10 is the appropriate and relevant sample size to use. • Data were available for N=7 patients at the 60-month timepoint in AADC-CU/1601. This is	page 37 (i.e. the number of participants we originally reported who were followed-up for each study is in line with the amended wording suggested by the company here). We do not believe we have made any factual errors. We have, however, decided to add further clarification about the numbers based on the company's suggested wording – we have added the following text to the bullet points related to studies AADC-010 and AADC-011 in section 3.2.1.5 of our report: AADC-010: "This is in line with the number of participants stated to be followed-up at Month 60 in CS Tables 14 and 15, which present results from the study." AADC-011: "This is in line with the number of participants stated in the

included in the ’60 month’ assessment, along with the ≥ 60-month data; this is unclear to the EAG). • AADC-011: ten participants, with assessments for the ‘12 month’ timepoint taking place between nine to ≥ 12 months (assuming that data at 9 to 12 months data was included in the ‘12 month’ assessment, along with the ≥ 12-month data; this is unclear to the EAG). • AADC-CU/1601: six participants (as stated in the CS) (note clarification response A10 suggests seven).”		the appropriate value to use. The Company would also like to reiterate that the denominator value for the primary endpoint is the number of enrolled patients (except AADC-011, which used N=10 as 2 patients could not attend follow-up due to COVID-19), not the number of participants assessed at each timepoint.	CSR results tables provided to the EAG in response to clarification question A19.”
Page 43: “There was some attrition, with discrepancies within or between the CS and the CSRs in regard to the number of patients lost (see section 3.2.1.5 and Table 55, Table 56 and Table 57), thus affecting completeness of follow-up. Results at 12 months in the AADC-011 trial	Replace statement with: “There was some attrition across the studies. All patients completed 12 months of follow-up, with 61% of the AADC-CU/1601 and AADC-010 combined population reporting 60 months of follow-up (see section 3.2.1.5 and Table 55, Table 56, and Table 57). Results at 12 months in the AADC-011 trial are reported out of 10 patients instead of the	The Company would like to note that two patients in AADC-011 could not attend follow-up visits due to COVID-10 travel restrictions. The analysis population was therefore changed to reflect the 10 patients who could attend follow-up visits. The suggested amendments provide to the text provide this clarity.	This is not an EAG factual inaccuracy. We have not made any errors in our reporting of the results and numbers of participants followed-up that were presented in CS Document B and CSR Table 9.

are reported out of the nine patients that presented for follow-up instead of out of 12 patients which would be the intent to treat (ITT) population. This affects the results when expressed as a proportion. For example, in CS section B.2.6.2.1 and CSR Table 9, [redacted] ([redacted]%) of patients are reported as achieving head control whereas if this was an ITT analysis, as per the other trial reports, it would be [redacted] ([redacted]) patients which is a smaller proportion. This is relevant when comparing results across the three trials, e.g. CS section B.2.6.2.2 states milestone achievement is comparable to that observed in the other trials for the same timepoint suggesting further improvement can be expected in later years after treatment. Thus there is a reporting bias for the results of this trial which favours the intervention."	12 patients which would be the intent to treat (ITT) population. This was because two patients could not attend follow-up due to COVID-19 travel restrictions. This affects the results when expressed as a proportion. For example, in Table 1, [redacted] ([redacted]) patients achieved full head control at Month 12, whereas if this was an ITT analysis as per the other trial reports, it would be [redacted] ([redacted]) patients. This is relevant when comparing results across the three trials, e.g., CS section B.2.6.2.2 states milestone achievement is comparable to that observed in the other trials for the same timepoint suggesting further improvement can be expected in later years after treatment. Thus, there is a potential reporting bias for the results of this trial which favours the intervention, although it should be noted that the Company has provided rationale for the change in the analysis population."		
Page 38, final paragraph:	Replace statement with:	Provides further clarity as to why there is a discrepancy in the CS	This is not a factual inaccuracy. We have

"Given the discrepancies noted in Table 8, it appears that at the '12 month' timepoint for study AADC-011, one participant is potentially unaccounted for in the CS. Two of the 12 enrolled participants could not attend an assessment, but results are presented for nine participants in the CS rather than 10. We note, however, that results for all 10 participants are reported in the CSR."	"Given the discrepancies noted in Table 8, it appears that at the '12 month' timepoint for study AADC-011, one participant was potentially unaccounted for in the CS. Two of the 12 enrolled participants could not attend an assessment, but results are presented for nine participants in the CS rather than 10. This discrepancy was due to the final AADC-011 tables and figures not being available at the time of the CS. We note that results for all 10 participants are reported in the final tables and figures from the CSR, data from which became available between the CS and the EAG clarification questions and were provided to the EAG as part of the clarification responses reference pack."	vs the final tables and figures from the AADC-011 CSR. The Company would like to clarify that the discrepancies were due to different versions of the AADC-011 CSR being available at the time of the CS vs EAG questions. Data were available for N=9 patients at the time of the CS (which used a draft final CSR for AADC-011). Final tables and figures from the final AADC-011 CSR were available at the time of EAG questions and included N=10 patients. The Company sent tables and figures from the final AADC-011 CSR to NICE in response to EAG question A19 (24 June 2022).	already noted in our report that results from all [redacted] participants are available in the CSR. We were not aware from the company's clarification response that the CSR tables and figures provided were "final tables and figures" as the company states in their suggested revised wording here. Company clarification response A19 does not state that the tables and figures were final. Furthermore, in clarification question A3, we asked the company if the updated version of the CSR was available and the company replied that "The final CSR for AADC-011 is not yet available. The company is therefore currently unable to provide a copy." Thus, we were not aware of what the reason for the discrepancy was. Please note that we have now marked up the

			following value in section 3.2.1.5, where we discuss follow-up, as we believe this should be marked up as CiC, as it came from the CSR: “We note, however, that results for all ■ participants are reported in the CSR.”
Page 52, First paragraph: “However, in study AADC-011 the primary endpoint was actually analysed using the number of patients who had the outcome assessed for the primary endpoint as the denominator. This biases the result toward favouring eladocagene exuparvovec.”	Replace statement with: “In study AADC-011, follow-up data could not be collected for 2/12 patients due to COVID-19 travel restrictions. The primary endpoint was therefore assessed using N=10 as the denominator, rather than N=12 value.”	Provides further clarity as to why there is a discrepancy in the CSR between the baseline population and follow up data. This point is clarified in **Error! Reference source not found.** and above. In AADC-011, two patients could not attend follow-up due to COVID-19 restrictions. The denominator for the primary endpoint was therefore N=10 instead of N=12.	This is not a factual inaccuracy, no change made. The EAG has correctly reported that the number of participants assessed was used as the denominator.
Page 54: “Second, that in study AADC-011 the primary endpoint (motor milestone achievement) was analysed using the number assessed for the outcome as the denominator rather than the	Replace statement with: “Second, it was also noted that 2 out of 12 patients in AADC-011 could not attend follow-up visits due to COVID-19. This meant that N=10 was used as the denominator for the primary endpoint analysis (motor milestone achievement).”	Provides clarity as to why there is a discrepancy in the CSR between the baseline population (N=12) and the denominator for the primary endpoint (N=10). The primary evidence from AADC-011 used the analysis population as the denominator	As stated above, this is not a factual inaccuracy. The EAG has correctly reported that the number of participants assessed was used as the denominator. However, as per our response to the point in the table row

number of participants at baseline. This biases the results in favour of eladocagene exuparvovec.”		(i.e. N=10) as it was not possible for 2 of 12 patients to attend follow-up visits due to COVID-19 travel restrictions. This point is also clarified in **Error! Reference source not found.** and above.	below, we have made a minor amendment to our conclusion about the potential bias this presents.
Page 52: “For all studies, the analysis populations for both efficacy and safety were to include all enrolled patients as all patients in each trial were treated with AAV2-hAADC gene therapy. However, in study AADC-011 the primary endpoint was actually analysed using the number of patients who had the outcome assessed for the primary endpoint as the denominator. This biases the result toward favouring eladocagene exuparvovec.”	Replace wording with: “For all studies, the analysis populations for both efficacy and safety were to include all enrolled patients as all patients in each trial were treated with AAV2-hAADC gene therapy. In study AADC-011, 2 out of 12 patients who could not attend follow-up visits due to COVID-19 travel restrictions. This meant that N=10 was used as the denominator for the primary endpoint analysis (motor milestone achievement).”	Provides clarity on the following statement: “However, in study AADC-011 the primary endpoint was actually analysed using the number of patients who had the outcome assessed for the primary endpoint as the denominator.” The Company argues that the N=10 population does not necessarily bias the results in favour of eladocagene exuparvovec. 	This is not a factual inaccuracy, so we have not amended the text using the company’s suggested wording. However, on reflection, the EAG has decided to add the word ‘could’ to the following sentence: “This *could bias* the result toward favouring eladocagene exuparvovec” to better reflect that this presented an uncertainty rather than a definitive bias.

		[redacted]	
On page 153, Table 57, row 6: Column 2: “9 of the 12 patients (75.0%) completed the follow-up at 12 months” Column 4: “At the primary efficacy analysis timepoint (12 months) only 10 out of 12 patients completed follow up (CSR Table 14.2.1.1.3) and data from 9 patients was included in the analysis (CS section B.2.6.2.1)”	Replace wording with: • Column 2: “[redacted] completed the follow-up at 12 months. Two patients were excluded from the analysis, leading to a baseline population of 10, as they could not attend follow-up due to COVID-19 travel restrictions.” • Column 4: “At the primary efficacy analysis timepoint (12 months) [redacted] completed follow up (Table 1). The two patients who did not attend follow-up were restricted by COVD-	Provides clarity on follow up data to reflect the following change: • The AADC-011 CSR was a draft version at the time of drafting the CS, so data for [redacted] patients were available. At EAG clarification questions, data from the final tables and figures from the AADC-011 CSR became available and included data for [redacted] patients (NB. The final CSR document was not available at the time of providing responses to	This is not a factual inaccuracy. The text in column 2 is the text provided by the company in CS Table 107. The EAG’s text in column 4 is accurate, but we have decided to provide further clarification and have amended it as follows: “At the primary efficacy analysis timepoint (12 months) only [redacted] (CSR Table 14.2.1.1.3) and data from [redacted] patients

	19, and therefore were excluded from analysis."	clarification questions). [redacted] is the appropriate and relevant sample size to use.	was included in the analysis *in* CS section B.2.6.2.1 *and from* [redacted] *patients in the CSR*". NB. We have now also marked up '[redacted] patients' in the 'EAG comments' column of Table 57 as AiC in our report, as the company's response here suggests it should be marked as such.

Issue 11 Discrepancies in clinical data N numbers in Table 16 (emerging or mastery)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58: Table 16. The Company would like to clarify the correct numbers in Table 16.	In line with the proposed changes in Issue 10, the Company proposes replacing Table 16 with Table **2** below. Changes include the following: • AADC-CU/1601 number assessed: Replaced values from CS section B.2.6.3.2 with values from Company clarification A10 Table 2. The previous values were not reflective of the precise number of patients assessed at each timepoint.	Table **2** and the edits to the text provide extra clarity and evidence on the following points: • Corrected the AADC-CU/1601 number assessed at each timepoint based on patient-level data on file (as provided in Company clarification A10). The values in CS section B.2.6.3.2 were not	This is not an EAG factual inaccuracy. The company's suggested corrections resolve discrepancies in the results data we identified between the CS and other data sources. We thank the company for clarifying which values are the correct ones to use. However, as the EAG believes that we have not

	• AADC-CU/1601 motor milestone achievement: No changes to the values reported in EAG clarification A10. These values are based on patient-level data on file. • AADC-011 number assessed: Values from AADC-011 CSR Table 14.2.1.3.3 selected for Month 12 over CS Table 20 to align with the latest data provided to the EAG during clarification questions. No changes to the Month 24 and 60 numbers. • AADC-011 motor milestone achievement: Month 12 values from AADC-011 CSR Table 14.2.1.3.3 value selected over CS Table 20 to align with the latest data provided to the EAG during clarification questions. Also, note added for denominator calculation with information provided on impact of COVID-19 on follow-up of two patients.	reflective of the precise number of patients assessed at each timepoint as they were based on time ranges rather than specific timepoint. • Confirmation that the most appropriate AADC-011 values are those from the final tables and figures from the final CSR (data from which were available at EAG clarification questions) rather than the CS. The evidence base increased from N=9 in the original CS to N=10 in • Table **2** and in the EAG clarification questions. Two patients were excluded as they could not attend follow-up due to COVID-19.	made any errors in our reporting in our Table 16, we have not replaced it with the company's revised table. We have, however, noted in section 3.2.5.1 of our report the following: "Please note that at the factual accuracy check stage of the appraisal, the company provided revised versions of Table 15 and Table 16, which included confirmation of which of the discrepant values were the correct ones to use (factual accuracy check Issues 10 and 11)." We have included this to sign-post the reader to these data for completeness.

Issue 12 Discrepancies in number of patients follow-up at each timepoint in the eladocagene exuparvovec studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 39: Table 8: Number of participants followed-up at timepoints in the eladocagene exuparvovec studies, row 2, column 2: "CS Table 10 states no participants withdrew or were lost to follow-up [e]" The Company would like to clarify the values in the table.	Replace wording with: "[redacted] [e]" Amend footnote e: "[e] Two patients could not attend the 12-month follow-up visit due to COVID-19."	Value and footnote updated to align with data from the final tables and figures from the AADC-011, which were made available between the CS and EAG clarification stages. The evidence base increased from [redacted] in the original CS to [redacted] in Table 2 and in the EAG questions.	This is not a factual inaccuracy. We have accurately reported information from the CS and CSR in this table. We have noted that the CSR results table (CSR Table 14.2.1.3.3) suggests [redacted] participants were followed-up. We do note, however, that we have made a minor typo in footnote e, where we have referred to "CS Table 14.2.1.3.3" rather than "CSR Table 14.2.1.3.3". We have now corrected this.
On page 39: Table 8: Number of participants followed-up at timepoints in the eladocagene exuparvovec studies, row 2, column 3: "[redacted] participants had data available beyond the 12-month trial period, including [redacted] participants with data at 60 months (clarification response	Replace wording with: "[redacted] participants had data available beyond the 12-month trial period, including [redacted] participants with data at 60 months (clarification response A21). Results were not included in the CS, but were provided in clarification response A21."	Provides clarity on follow up data across the trials, to correct a typographical error in clarification response A21. The number of participants with data at 60 months was incorrectly reported in clarification response A21 due to a typographical error	This is not the EAG's error, but we have noted the correct value in Table 8 by including the following statement: "please note, at the factual accuracy check, the company stated they had reported this value [redacted] in error and that [redacted]

A21). Results were not included in the CS, but were provided in clarification response A21." The Company would like to clarify the values in the table.		(reported [redacted] participants, correct value [redacted] participant).	participant was followed up at 60 months
On page 38, paragraph 2: "Given the discrepancies noted in Table 8, it appears that at the '12 month' timepoint for study AADC-011, one participant is potentially unaccounted for in the CS. Two of the 12 enrolled participants could not attend an assessment, but results are presented for nine participants in the CS rather than 10. We note, however, that results for all 10 participants are reported in the CSR. Inclusion of the participant missing from the CS makes the results for eladocagene exuparvovec more favourable (see section 3.2.5.1), so this is not an issue."	Remove mention of the "one unaccounted participant". Suggested replacement wording: "As stated in Table 8, for the '12 month' timepoint for study AADC-011, two of the 12 enrolled participants could not attend the Month 12 assessment due to COVID-19 travel restrictions. Results for all 10 participants are reported in the final tables and figures from the CSR, which were made available to the Company and EAG at the clarification questions stage."	Reflects the Company's proposed changes to Table 8 in the EAG report and reflects that there are no unaccounted patients at Month 12 in the final tables and figures of the AADC-011 CSR. The final tables and figures of the AADC-011 CSR were made available between the CS and EAG clarification stages. The evidence base increased from N=[redacted] in the original CS to N=[redacted] in Table 2 and in the EAG questions.	None of the data reported in this paragraph are factually inaccurate. We have already acknowledged that results for all [redacted] participants are provided in the CSR. We have, however, decided to clarify our meaning in the paragraph, by making it clear that the EAG determined that one participant is potentially unaccounted for (rather than stating it "appears" one is unaccounted for) and by clarifying that where we refer to the "CS", we specifically mean "CS Document B".

Issue 13 Treatment waning scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Page 140 states: "There is uncertainty in the persistence of treatment benefit in the long term. The EAG notes the lack of long-term data beyond 10 years to inform whether the treatment benefit of eladocagene exuparvovec persists over time or patients decline at any point (see section **Error! Reference source not found.**). Therefore, although we assume no treatment waning in our preferred base case, we explore several scenarios assuming a decline in treatment effect (gradual decline from year 25 onwards, between year 25 and 35 or a sudden decline at year 25)." • Page 132, Table 48, "Treatment waning" row	The Company requests that the waning scenarios are removed from the EAG scenario analyses from section 4.2.6.3, Table 48, Table 49 and Table 52, and that all associated references to treatment waning scenarios are removed from Pages 132, 134, 135, 137 and 141. The treatment waning scenario is hypothetical and is not consistent nor reflective of the clinical data and clinical expert advice.	The Company considers a waning scenario to be unrealistic and should not be considered as part of the appraisal. The EAG notes that this was a pessimistic scenario in HST15 and, moreover, was not considered under the NICE Committee's preferred assumption, suggesting it is inappropriate for this appraisal. Evidence in patients treated with eladocagene exuparvovec indicates that patients retain motor function in the long-term. In addition, insights from the EAG report support that a decline in motor function is unlikely. The EAG report Section 2.2.1.3 states that the "EAG acknowledge that people with AADC deficiency do not generally show a deterioration in their symptoms over time" and the EAG's clinical expert stated that "in fact many do make limited developmental progress". In fact, the EAG	Not a factual inaccuracy. In EAG report Section 4.2.6.3, it is clearly stated that we explored a series of '*conservative exploratory scenarios'* to test the impact on the cost-effectiveness results, should the treatment effectiveness of eladocagene exuparvovec wane in the long-term horizon. None of these hypothetical scenarios impact the EAG preferred assumptions. For clarity, we have revised the text in Page 140 to include the term 'exploratory', as shown below: "Therefore, although we assume no treatment waning in our preferred base case, we explore several <u>exploratory</u>

• Page 134, Table 49, all four "Treatment waning" rows • Page 135: "Other scenarios that influence the base case ICER (at a discount rate of 3.5%) include: treatment waning assumptions, use of the lower and upper credible interval estimates for the cumulative ordered logit model…" • Page 137 states: "…the approach used to impute missing data for the observed distribution of patients across motor milestones (based on LOCF, original sample or distribution per follow-up), treatment waning and health state utility values." • Page 138, Table 52, all four "Treatment waning" rows • Page 137 states: "…for the observed distribution of patients across motor milestones (that is, based on original sample, distribution per follow up or LOCF), treatment waning		report states: "Clinical advice to the EAG is that, due eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time." (Page 67 of EAG report). This highlights that waning is unlikely with eladocagene exuparvovec. In addition to the clinical data supporting that waning is unrealistic, there is clear biologic rationale. Eladocagene exuparvovec is a gene replacement therapy that restores AADC enzyme functioning, irrespective of genotype. Clinical data show that AADC enzyme functioning is retained throughout the clinical trials, as shown by sustained dopamine production. In addition, the EMA note in their assessment report that the eladocagene exuparvovec vector "has the ability to confer long-term stable gene expression without associated inflammation or toxicity."	scenarios assuming a decline in treatment effect (gradual decline from year 25 onwards, between year 25 and 35 or a sudden decline at year 25)." In Page 135, we have included the term 'exploratory' for clarity in the following text: "Other scenarios that influence the base case ICER (at a discount rate of 3.5%) include: exploratory treatment waning assumptions,….." In Page 137, we have revised the text as "…. for the observed distribution of patients across motor milestones (based on LOCF, original sample or distribution per follow-up), exploratory treatment waning assumptions and health state utility values."

and health state utility values."		Taken together, the evidence show that treatment effect is persistent and maintained. As such, it is not clinically plausible to suggest that the treatment effect would wane in the long-term.	
Page 104 states: "EAG conclusions**:** Consultation with our clinical expert suggests that there is uncertainty regarding persistence of treatment effect in the long term due to lack of longer follow up data. We also note that in a previous NICE HST-15, a pessimistic scenario was conducted where patients with spinal muscular atrophy, a proxy disease to AADC deficiency, were assumed to regress from higher to lower functioning health states after 25 years of treatment. We conducted similar conservative exploratory scenarios to test the impact on the cost-effectiveness results, should the treatment effectiveness wane in the long-term horizon (see Section **Error! Reference**	As above, the Company requests that the waning scenario is removed from the EAG scenario analysis. Suggested replacement text: "EAG conclusions: Consultation with our clinical expert suggests that there is uncertainty regarding persistence of treatment effect in the long term due to lack of longer follow up data."	In line with the above, the Company does not agree that a waning scenario is plausible based on the available clinical evidence.	Not a factual inaccuracy. Therefore, no change to text. Please refer to our comments above.

source not found. of this report)."			

Issue 14 Pre- and post- administration resource use and costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 110 states: "Post-surgery, the paediatric intensive care unit stay should be costed, on average, for at least two days in intensive care and the paediatric ward stay for five days, to reflect clinical practice, as stated above." The EAG costed the paediatric intensive care unit and the paediatric ward stay as per day within the economic model.	The Company requests that the EAG provide rationale, references, and/or the accompanying calculations to justify the assumption that costs sourced from the National Schedule of Reference Costs for a paediatric intensive care unit stay and paediatric ward stay are *per day* and not *per stay*.	The Company are under the assumption that the costs sourced from the National Schedule of Reference Costs are given for *per stay* with the exception of excess bed days. The Company therefore believes the EAG model may be incorrect. More information is needed to verify this.	Not a factual inaccuracy. Hence, no change to text and no model update. The costs of £3,305.99 and £3,064.90 for Paediatric ICU (XB03Z) and Paediatric ward stay (XB01Z), respectively, are national average unit costs as obtained from Sheet!CC of the National Schedule of NHS Costs- Year 2019-20. Based on this information, the EAG assumed these average unit costs as costs incurred per day in the EAG analyses.

Issue 15 EAG's preferred base case

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 88 states: "Based on our clinical expert's advice the baseline characteristics are reflective of clinical practice, except the mean age of the modelled population is lower than expected in clinical practice." Page 21 and 135 states: "The EAG preferred model assumptions are as follows: 1. Baseline age and weight of population: 6 years and 15 kg" Page 131, Table 48, "Population" row, "ERG preferred" column states: "6 years, 15 kg" Page 22, Table 4, and Page 136, Table 50:	The Company requests that the EAG provides a reference or additional information for their preferred base case assumption of a baseline age of 6 years and baseline weight of 15kg. No reference or information was provided in the EAG report.	This EAG's preferred base case is based on clinical expert advice that a mean age of 4 years is lower than expected in clinical practice. Other than this, the EAG provide no reference for their preferred model assumption of a mean age of 6 years and a mean weight of 15kg. For this reason, the Company considers the EAG's preferred approach to be inappropriate. The Company therefore requests for more information to determine the validity of the EAG preferred assumptions. The Company believes a mean age of 4 years and mean weight of 11.1kg is more appropriate and representative of the eligible population than the EAG preference as it is derived directly from the eladocagene exuparvovec trials (see section B.2.3.1.1 and section B.3.2.1 of the CS)[13–15] and corresponds directly with the efficacy data.	Not a factual inaccuracy. Therefore, no change to text on Pages 88, 21, 135, 131 (Table 48), 22 (Table 4), and 136 (Table 50). Our base case assumption of using a baseline average age of 6 years was based on advice from our clinical expert who stated that the ages of the patients they treat range between 2 and 14 years. With respect to the associated average weight, our expert advised that people with AADC deficiency tend to be within the lowest centiles for their ages, compared to their peers. Therefore, we used the average weight from the lowest quantile (0.4^{th}) for those aged 6 years, which is 15 kgs. This information is obtained from the UK-WHO Growth Charts 2009 of boys and

"+ Age and weight: 6 years and 15 kg"		The Company also notes that the EAG's clinical expert could not comment on whether the trial population baseline weight was representative of the UK population baseline weight (page 41 of EAG report), and the EAG's clinical expert also said the trial population was "generally representative of the people with AADC deficiency seen in clinical practice." (page 42 of EAG report). While we acknowledge that patients may be diagnosed later in the UK than in Taiwan, the pathway of care incorporating eladocagene exuparvovec in the clinical setting will aim to identify, diagnose and treat patients when they are as young as possible as this may allow patients to gain the full effects of the technology. This is supported in the marketing authorization granted by the EMA which states that "the treatment effect tends to be more pronounced in children who are younger".[3]	girls aged between 4-20 years. For completeness, we conducted additional scenarios both on the EAG corrected company's revised cost effectiveness model as well as the EAG preferred cost-effectiveness model, where we varied the mean age and weight of the population as shown in Table 49, Page 135, and Table 52, Page 139, respectively of the EAG report.

Page 133, Table 48, “Number of carers” row, “EAG preferred” column states: “Yes”	The company propose the text is amended from “Yes” to: “No motor function: 2.5 carers Other motor milestone health states: 2 carers”	Provides clarity on the EAG’s preferred base-case setting for the number of carers included in the cost-effectiveness analysis.	Thank you for highlighting this. Not a factual inaccuracy. However, for clarity we have revised the text in Page 133, Table 48 as proposed by the company.

Issue 16 OGC episodes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 63, Table 18: The Company would like to flag that the value in the CS were incorrect due to the use of a draft version of the final CSR for AADC-010 during development of the submission.	Replace Table 18 with **Table 3**.	Provides clarity on OGC hours per week values in AADC-010, replacing draft CSR values with final CSR values. Values in the CS were from a draft version of the final CSR for AADC-010 and contained errors. The final CSR was made available very close to the submission deadline, so the numbers reported in the CS for OGC episodes were not updated. The replacement table uses values from the finalised version of the CSR, which is correct and therefore most relevant to use.	This is not the EAG’s error. We have, however, added the following text to section 3.2.5.3 of our report to inform the reader that the values in Table 18 are incorrect and the correct values are provided by the company in the factual accuracy check: “Please note that at the factual accuracy check stage of the appraisal, the company clarified that the data they had provided in the CS were incorrect and they thus provided a revised version of Table 18, with

			corrected values, in factual accuracy check Issue 16)."
On page 62: "Table 18 reports summary statistics for time patients experienced oculogyric crisis in hours per week following eladocagene exuparvovec treatment in study AADC-010. This showed a gradual reduction in oculogyric crises in hours per week over time (with a reduction from baseline by a mean of [redacted] hours per week at 3 months (n=[redacted]), [redacted] hours per week at 6 months (N=[redacted]), [redacted] hours per week at 9 months (n=[redacted]), and [redacted] hours per week at 12 months (n=[redacted])."	Replace wording with: "Table 18 reports summary statistics for time patients experienced oculogyric crisis in hours per week following eladocagene exuparvovec treatment in study AADC-010. This showed a gradual reduction in oculogyric crises in hours per week over time (with a reduction from baseline by a mean of [redacted] hours per week at 3 months (N=[redacted]), [redacted] hours per week at 6 months (N=[redacted]), [redacted] hours per week at 9 months (N=[redacted]), and [redacted] hours per week at 12 months (N=[redacted])."	As above, numbers updated to reflect the final CSR values.	This is not the EAG's error, and so we have not amended our report. We thank the company for clarifying that the data they provided were incorrect.

Issue 17 Eladocagene exuparvovec dosing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 42, paragraph 2: "The trials' populations and the doses of eladocagene exuparvovec used adequately	Replace the text with: "The trials' populations and the doses of eladocagene exuparvovec used adequately reflect the proposed licensed	Provides further clarity on the statement. As stated in the EMA assessment report[3] and SmPC[2],	This is not a factual inaccuracy. We have already acknowledged in section 3.2.1.3 that the draft SmPC states that

reflect the proposed licenced indication, even though nine participants in one study received a higher dose than indicated in the proposed SmPC."	indication. Though nine participants in one study received a higher dose than indicated in the SmPC, the EMA concluded that the two doses had comparable efficacy and safety (CS section B.2.2), as stated in the SmPC[2] and EMA assessment report.[3] Clinical expert advice to the EAG is that combining the results from both doses is reasonable"	the two doses were deemed to have comparable efficacy and safety.[3]	[redacted]. Furthermore, we have also provided advice in our report from our expert that combining the results from both doses is reasonable. We have, however, decided to further clarify in our statement to which the company refers that we did not identify an issue with the company's approach, by amending the text as follows: "The trials' populations and the doses of eladocagene exuparvovec used adequately reflect the proposed licenced indication, even though nine participants in one study [redacted] *(for the reasons discussed above, we do not believe that this is an issue)*."

Issue 18 Genotype / phenotype correlation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 42, paragraph 1: "The gene therapy delivers a complete copy of the missing AADC gene and is not specific to any genetic mutation, so theoretically the genotype should not matter, although this has not been tested in the trials. The EAG's clinical expert suggested that ideally the gene therapy should be tested on a broad spectrum of AADC genotypes" The Company would like to point out that there is currently limited evidence to show that genetic mutation impacts disease or treatment outcomes, as stated by clinical experts consulted as part of this appraisal.	Replace the text with: "The gene therapy delivers a complete copy of the missing AADC gene and is not specific to any genetic mutation, so theoretically the genotype should not matter, although this has not been tested in the trials. The EAG's clinical expert suggested that ideally the gene therapy should be tested on a broad spectrum of AADC genotypes. The EAG acknowledge that, given the ultra-rare nature of AADC deficiency, it is likely to be challenging to generate evidence across a broad spectrum of AADC genotypes."	Provides further clarity on the statement: "Although this has not been tested in the trials." The Company would like to note that there is limited evidence that genotype influences phenotype or disease/ treatment outcomes. The Company would also like to note that the rarity of AADC deficiency makes it challenging to recruit across a broad range of genotypes. The Company therefore proposes an amendment to the EAG's wording to reflect this	This is not a factual inaccuracy, no change made.
On page 41, paragraph 2: "All patients in the company trials had the founder mutation which is prevalent in east Asian patients with the	Replace text with: "All patients in the company trials had the founder mutation, which is prevalent in east Asian patients with the disease. Whilst our clinical expert explained that none of their	As above, provides further clarity on statement and incorporates relevant clinical opinion on the link between genotype and phenotype.	This is not a factual inaccuracy, no change made.

disease. Whereas our clinical expert explained that none of their patients in the UK (including those referred from Europe) had the founder mutation."	patients in the UK (including those referred from Europe) had the founder mutation, as stated in CS Section B.2.3.1.1 and as per clinical opinion and published consensus guidelines,[1] there is limited evidence linking genetic mutation to disease or treatment outcomes."		
Page 80, paragraph 1: "The eladocagene exuparvovec trial participants were generally representative of the people with AADC deficiency seen in clinical practice, except for race and, associated with this, genotype (all the participants had the founder mutation)."	Replace wording with: "The eladocagene exuparvovec trial participants were generally representative of the people with AADC deficiency seen in clinical practice, except for race and, associated with this, genotype (all the trial participants had the founder mutation). It should be noted that there is no evidence linking genotype and disease/treatment outcomes"	As above, clarifies that there is no link between genotype and phenotype, disease progression, or treatment outcomes. The Company would like to note that eladocagene exuparvovec replaces the deficient AADC gene regardless of the genotype, so is genotype-agnostic. The Company would also like to note that the rarity of AADC deficiency makes it challenging to recruit across a broad range of genotypes.	This is not a factual inaccuracy, no change made.
On page 81, bullet 3: "All participants in the trials had the founder mutation. It is unknown if genotype might impact on clinical effectiveness of eladocagene	Replace text with: "All participants in the trials had the founder mutation. There is, however, limited evidence linking genetic mutation to disease or treatment outcomes as stated in CS Section B.2.3.1.1 and as per clinical	As above, clarifies that there is no link between genotype and phenotype, disease progression, or treatment outcomes.	This is not a factual inaccuracy, no change made.

exuparvovec, as no evidence is available, but theoretically it may not. Nonetheless, clinical expert advice to the EAG is that ideally the gene therapy should be tested on a broad spectrum of AADC genotypes."	opinion and published consensus guidelines.[1] Nonetheless, clinical expert advice to the EAG is that ideally the gene therapy should be tested on a broad spectrum of AADC genotypes. It should be noted that the rare nature of the disease and limited patient population restricted the feasibility to test a broad spectrum of genotypes."	Provides further clarity on statement and incorporates relevant literature and clinical opinion on the link between genotype and phenotype, as well as providing rationale for the evidence base.	

Issue 19 Comparability of the NHDB with eladocagene exuparvovec studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 75, second bullet point on page: "It is unclear if the 49 participants included in the NHDB CS analyses were sufficiently comparable to those included in the eladocagene exuparvovec studies."	Replace the text with: "Aside from comparability in terms of disease severity, it is unclear if the 49 participants included in the NHDB CS analyses were sufficiently comparable to those included in the eladocagene exuparvovec studies."	Improves clarity and accuracy of the statement. The Company would like to clarify that the comparability in terms of severity between the N=49 NHDB population and the participants in the eladocagene exuparvovec studies has been discussed and demonstrated in the CS and this is an important and relevant factor in determining comparability.	We agree that the company's proposed amendment improves the clarity and accuracy of the statement. We also note it reflects our statement in section 3.3.3 that "Disease severity (the severe phenotype) was defined essentially the same in the NHDB and eladocagene exuparvovec studies". We have therefore amended the text as suggested by the company.

Issue 20 Critical appraisal

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 44 and 45: Table 9, Table 10, Table 11 - Was the outcome accurately measured to minimise bias? – EAG response: "Probably"	The Company requests that "probably" is replaced with "yes".	As noted in EAG report Table 55, 56, and 57: "Blinding to treatment exposure was not possible, however bias was minimised as outcomes were measured using objective, validated measurement tools and follow-ups were carried out per protocol. No centralised assessment or independent clinical verification was reported for any of the outcomes." Based on this information, the Company considers the appropriate answer to therefore be "Yes", as the EAG's rationale provides limited evidence their response.	This was the EAG's judgement and thus this is not a factual inaccuracy. We have reviewed our justification for our judgement and we have decided not to change it to 'yes', due to the uncertainties already noted in the justification.
Page 148, 150 and 152: Table 55, Table 56 and Table 57 - Was the outcome accurately measured to minimise bias? – EAG response: "Probably"	The Company requests that "probably" is replaced with "yes".	As per justification in the row above, the Company considers the appropriate answer to be "yes".	Please see our response above. This is not a factual inaccuracy; no change made.

Issue 21 NHDB systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 71, final bullet point on page: "The CS systematic review searches were more restricted than those of Bergkvist et al. (2021)."	Replace the text with: "The CS systematic review searches were conducted in line with NICE guidance and had a different scope to those of Bergkvist et al. (2021)."	Improves clarity of the statement and reasons for the difference in scope of the systematic searches in Bergkvist versus the CS. The Company would like to clarify that the CS systematic review was conducted in line with NICE guidance and the differences were due to a different scope to the Bergkvist et al. searches.	This is not a factual inaccuracy; no change made. The EAG believes that the CS searches may not have identified case reports, thus resulting in an uncertainty whether all recently published evidence has been captured.
Page 71, second bullet point on page: "There is, however, a lack of clarity in the CS and in Bergkvist et al. (2021)[23] about whether two independent reviewers screened publications at the full text screening stage. If this approach was not used, there is a risk of bias in the selection of the evidence to include in the NHDB."	Replace the text with: "As two independent reviewers screened publications at the full text screening stage, there is a low risk of bias in the selection of the evidence to include in the NHDB."	Improves clarity and accuracy of the statement. The Company confirms that two independent reviewers screened publications at the full text screening stage, as detailed in D1.1.8 in the CS.	This is not a factual inaccuracy; no change made. The EAG has reviewed CS appendix D1.1.8 and we cannot find an explicit statement that two independent reviewers screened publications at the full text screening stage. In the 'Selection process' section of this CS appendix, the text states: "Two independent reviewers screened the results from the database

			searches for eligibility and inclusion of publications into the review. A third independent reviewer adjudicated any discrepancies." It is unclear to us if this means that two independent reviewers screened full text publications.
Page 72, third bullet point on page: "It remains unclear to the EAG why the data included in (Pearson et al., 2020)[24] and Williams et al. (2021)[27] was considered insufficient for use in the NHDB. This is because we understand from clarification response A39, that motor function results from studies were entered into the database "as is" from studies and two independent clinical experts used these data to determine the motor milestone achievement results (i.e. those pooled in CS Table 29). It is unclear why the data	Replace the text with: "The Company has clarified during the clarification questions that the reason for the exclusion of Pearson et al., 2020)[24] and Williams et al. (2021)[27] was due to the study type where data was collected indirectly via questionnaires, including the use of online questionnaires with data combined with answers from parents and caregivers in the case of Pearson et al., 2020,[24]. It remains unclear to the EAG why the data included in (Pearson et al., 2020)[24] and Williams et al. (2021)[27] were considered insufficient for use in the NHDB"	Improves clarity and accuracy of the statement based on the information provided by the Company. The Company would like to clarify that the rationale for excluding these studies was provided in both question A27, Table 8, and question A29 in the EAG questions. The studies were excluded due to the type of study, where they are designed as questionnaires.	This is not a factual inaccuracy, but the EAG has nonetheless amended our report to provide the reasons from the company's clarification response A37 as to why the two studies were excluded. We have amended the text as follows: "It remains unclear to the EAG why the data included in (Pearson et al., 2020)[24] and Williams et al. (2021)[27] was considered insufficient for use in the NHDB. *The company clarified that these studies were excluded as data were collected via questionnaires, including*

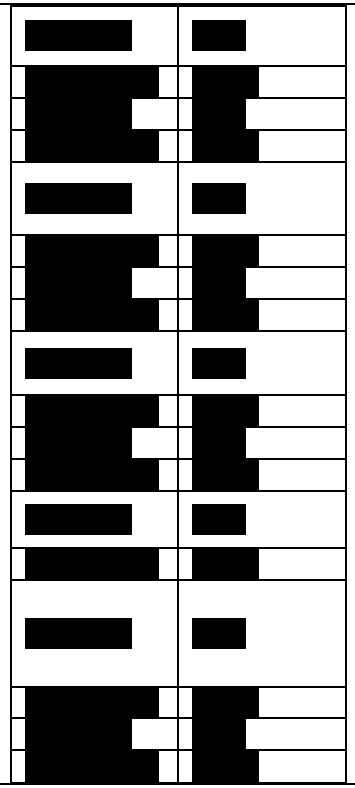
in these two studies could not be used for this purpose.”			*the use of online questionnaires with data combined with answers from parents and caregivers in the case of Pearson et al. 2020 (clarification response A37). Given that* we understand from clarification response A39, that motor function results from studies were entered into the database “as is” from studies and two independent clinical experts used these data to determine the motor milestone achievement results (i.e. those pooled in CS Table 29), *it remains* unclear *to the EAG* why the data in these two studies could not be used for this purpose. This raises the possibility that not all relevant publications, and thus not all unique individuals with ADDC deficiency, were included in the NHDB.”

Issue 22 Systematic literature review methodology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 34, Table 6: "Was data extraction performed by two or more reviewers independently? No"	Change the following text in the EAG report from: • "No" to "Yes"	Provides clarity on the methodology: As stated in CS section D1.1.2: "Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers or by consulting a third reviewer if necessary." This involvement of a 2nd and 3rd reviewer, for accuracy checking and discrepancy resolution, constitutes involvement in the 'data extraction' process, warranting a 'Yes' in answer to this question.	This is not a factual error; this is the EAG's judgement. Two or more reviewers did not independently perform data extraction (i.e. they did not separately perform this task, without sight of the others' data extraction). As stated by the company in CS section D.1.1.2, one reviewer extracted data and the other checked it. We have noted that this was the process used in our 'EAG comments' column in Table 54, which provides the rationale for the EAG's judgement. As stated in the table, the EAG finds the data extraction process used acceptable.

Confidentiality corrections

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 62	The number of patients experiencing reduced oculogyric crisis activity at different time points. These numbers should be marked up as academic in confidence (AiC) as per the Company model.	"This showed a gradual reduction in oculogyric crises in hours per week over time (with a reduction from baseline by a mean of [redacted] hours per week at 3 months (n=[redacted]), [redacted] hours per week at 6 months (N=[redacted]), [redacted] hours per week at 9 months (n=[redacted]), and [redacted] hours per week at 12 months (n=[redacted])." "However, only data up to 3 months was reported. Oculogyric crisis activity reduced from baseline by [redacted] hours per week at 1 month (n=[redacted]), [redacted] hours per week at 2 months (n=[redacted]) and [redacted] (n = [redacted]) hours per week at month 3."	Thank you for highlighting this. We have now amended the marking.
Page 22, Table 4 Page 136, Table 50	The total costs and total QALYs for BSC have not been marked up within Table 4 and Table 50. These numbers should be marked up as commercial in confidence (CiC) as per the Company model.	The remaining values in Table 4 and Table 50, "Total costs" and "Total QALYs" columns, need to be marked up with CiC. **Total costs**: **3.5%** **Total QALYs**: **3.5%**	Thank you for highlighting this. We have corrected the CiC markings in Table 4 and Table 50.

			
Page 39, Table 8	The number of patients at follow-up at each time point for each trial should be marked up as academic in confidence (AiC) as per the Company model.	The following values should be marked-up with AiC: "AADC-010 n=10" row, "Up to 12 months" column: [redacted] ([redacted]%) "AADC-010 n=10" row, "Up to 24 months" column:	Thank you for highlighting this. We have now amended the marking.

		[redacted] ([redacted]%) "AADC-CU/1601 n=8" row, "Up to 12 months" column: [redacted] ([redacted]%) "AADC-CU/1601 n=8" row, "Up to 24 months" column: [redacted] ([redacted]%)	
Page 65, Table 20	The number of patients experiencing the most common adverse events. These numbers should be marked up as academic in confidence (AiC) as per the Company model and CS table 32.	**Patients N (%)** [redacted]	Thank you for highlighting this. We have now amended the marking.

(Please add further lines to the table as necessary)

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 76, first section subheading 3.4.1: "Data inputs to the NMA"	Replace text with: "Data inputs to the ITC"	Improves clarity and accuracy of the statement. The Company would like to clarify that they did not carry out a network meta-analysis (NMA) as there was only two	We thank the company for pointing out this error; we have now amended the sub-heading in line with the proposed

		comparators available. Instead, the Company looked at the feasibility of an indirect treatment comparison (ITC) to evaluate whether a robust ITC could be conducted.	amendment suggested by the company.
Page 77, second section subheading 3.4.2: “Statistical methods for the NMA”	Replace text with: “Statistical methods for the ITC”	Improves clarity and accuracy of the statement. The Company would like to clarify that they did not carry out a network meta-analysis (NMA) as there was only two comparators available. Instead, the Company looked at the feasibility of an indirect treatment comparison (ITC) to evaluate whether a robust ITC could be conducted.	We thank the company for pointing out this error; we have now amended the sub-heading in line with the proposed amendment suggested by the company.
Page 77, first paragraph: **“**The analysis including sex alone yields a higher ESS (29.8)” This is a rounding error, as the remainder of the numbers in this paragraph are rounded to two decimal places.	Replace text with: **“**The analysis including sex alone yields a higher ESS (29.81)”	Typographical error.	We thank the company for pointing out this error; we have now amended the number to “29.81” as suggested by the company.

Page 92: "The median estimate obtained by the company for the cumulative ordered logit models that used PDMS-2 scores as a covariate was [redacted] (95% Credible Interval: [redacted])."	The Company propose the EAG amend text to: "The median estimate obtained by the company for the cumulative ordered logit models that used PDMS-2 scores as a covariate was [redacted] (95% Credible Interval: [redacted])."	Correction of the value "[redacted]", which should state "[redacted]"	Thank you for highlighting this. We have corrected the typographical error. We have also now marked these data as CiC, as they were not marked as such in our original report.
Page 98 states: "We also did not identify any inconsistencies in the survival probabilities reported in Brooks et al and the economic model."	The Company propose the text is amended to: "We also did not identify any inconsistencies in the survival probabilities reported in Brooks et al. and the economic model."	Typographical error: the '.' was missing after "Brooks et al.".	Thank you for highlighting this. We have corrected the typographical error.
Page 108: "EAG conclusions: The study by Tai et al[1] retrospectively collected 17 carers'…"	The Company propose the text is amended to: "EAG conclusions: The study by Tai et al.[1] retrospectively collected 17 carers'…"	Typographical error: the '.' was missing after "Tai et al.".	Thank you for highlighting this. We have corrected the typographical error.
Page 40, 1st bullet:	The Company propose the text is amended to:	Typographical error: the 'a' was missing after "(N=15) is".	Thank you for highlighting this. We have corrected the typographical error.

"AADC-1602 (N=15) is long-term efficacy and safety study…"	"AADC-1602 (N=15) is a long-term efficacy and safety study…"		
Page 46, Table 12, 2nd row: "Walking with assistance[h] up to 12 months (AADC-011)/ 60 months (AADC-010 AADC-1601))"	The Company propose the text is amended to: "Walking with assistance[h] up to 12 months (AADC-011)/ 60 months (AADC-010, AADC-1601)"	Typographical error: the ',' was missing after "AADC-010". Typographical error: an extra ')' was included after "AADC-1601".	Thank you for highlighting this. We have corrected the typographical error.
Page 46, Table 12, 3rd row: "Raw scores for the PDMS-2 subscales[i] up to 12 months (AADC-011)/ 60 months (AADC-010[j] AADC-CU/1601)"	The Company propose the text is amended to: "Raw scores for the PDMS-2 subscales[i] up to 12 months (AADC-011)/ 60 months (AADC-010[j], AADC-CU/1601)"	Typographical error: the ',' was missing after "AADC-010".	Thank you for highlighting this. We have corrected the typographical error.
Page 47: "An additional outcome assessed in all three trials and reported in the CS, but not included in the NICE final scope was change from baseline in.."	The Company propose the text is amended to: "An additional outcome assessed in all three trials and reported in the CS, but not included in the NICE final scope, was change from baseline in…"	Typographical error: the ',' was missing after "CS".	We believe the company means that the ',' was missing after "scope". Thank you for highlighting this. We have corrected the typographical error.
Page 50: "Our expert agreed that the definitions of these outcomes	The Company propose the text is amended to:	Typographical error: changed "was" to "were".	Thank you for highlighting this. We have corrected the typographical error.

used in the trials was reasonable”	“Our expert agreed that the definitions of these outcomes used in the trials were reasonable”		
Page 66: “She notes that this would be managed by: a reduction and weaning off of dopaminergic medications; carefully monitored sedation (e.g. benzodiazpeines);”	The Company propose the text is amended to: “She notes that this would be managed by: a reduction and weaning off of dopaminergic medications; carefully monitored sedation (e.g. benzodiazepines);”	Typographical error: Incorrect spelling of “benzodiazepines”.	Thank you for highlighting this. We have corrected the typographical error.
Page 131, Table 48, “ERG preferred” column.	The Company propose the label of the column is amended to “EAG preferred”.	To align with the reference of ‘EAG’ throughout rest of the report.	Thank you for highlighting this. We have corrected the typographical error.

Appendix: Corrected data tables from the EAG report

Table 1: Cumulative key motor milestone achievement (mastery, i.e. score of 2 on relevant PDMS-2 item) up to that timepoint[b]

Motor milestone	Timepoint	AADC-CU/1601 (N=8)		AADC-010 (N=10)		AADC-011 (N=12) [g]	
		No. assessed[a]	No. patients (%)[b,c]	No. assessed[e]	No. patients (%)[b,c]	No. assessed	No. patients (%)[b,c]
No motor function	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full head control (PDMS-2 item #10)	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting unassisted (PDMS-2 item #14)	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support (PDMS-2 item #28)	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with assistance (PDMS-2 item #34)	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR, not reported.
[a] Based on data from Table 2 from Company clarification A10 (which is based on data on file generated to respond to the EAG clarification question)
[b] As per the primary endpoint in each study, the number of patients reported is the cumulative number who had achieved mastery of that PDMS-2 item up to the timepoint of assessment.
[c] The % is calculated using the baseline population as the denominator, with the exception of AADC-011. In AADC-011, two patients could not attend follow-up due to COVID and so the denominator is N=10.
[d] Based on data from Table 4 of the AADC-CU/1601 CSR (also reported in Table 25 of the Company submission)
[e] Based on data from Table 14.2.1.3 of the AADC-010 CSR
[f] Based on data from Table 14.2.1.2 of the AADC-010 CSR (also reported in Table 14 of the Company submission)
[g] Not all subjects were able to return to the clinic for follow-up; as such, only 10 of the 12 enrolled subjects were assessed at Month 12. Subjects 011-311 and 011-313 were unable to return to the investigational site after Month 6 due to COVID-19 travel restrictions. At the Month 6 Visit, the highest motor milestone achieved by Subject 011-311 was standing with support (score of 2, mastery). Subject 011-313 had not achieved any motor milestones by the Month 6 Visit.
[h] Based on data on file generated to support the Company response to clarification question A21.
[i] Based on data from Table 14.2.1.1.3 of the AADC-011 tables and figures provided to the EAG at clarification questions
j CS Table 25 previously stated proportion of [redacted] to 1 decimal place; The company agree with EAG calculation of [redacted] (i.e. [redacted]) to 2 decimal places, using baseline denominator
[k] Results up to 60 months are reported in clarification response A21, but exact numbers of participants achieving each motor milestone at each timepoint is not reported.
[l] CS Table 14 previously stated [redacted] which was a typographical mistake; The company agree with EAG calculation of [redacted], using the baseline denominator.

Table 2: Cumulative key motor milestone achievement (newly emerging or mastery i.e. score of 1 or 2 on relevant PDMS-2 item) up to that timepoint

Motor milestone	Timepoint	AADC-CU/1601 (N=8)		AADC-010 (N=10)		AADC-011 (N=12)	
		No. assessed [a]	No. patients (%)[b, h]	No. assessed [d]	No. patients (%)[b, c]	No. assessed	No. patients (%)[b]
No motor function	Baseline						
Full head control (PDMS-2 item #10)	Baseline						
	Month 12						
	Month 24						
	Month 60						
Sitting unassisted (PDMS-2 item #14)	Baseline						
	Month 12						
	Month 24						
	Month 60						
Standing with support (PDMS-2 item #28)	Baseline						
	Month 12						
	Month 24						
	Month 60						
Walking with assistance (PDMS-2 item #34)	Baseline						
	Month 12						
	Month 24						
	Month 60						

Sources: AADC-010 CSR Table 14.2.1.3, AADC-011 CSR Table 14.2.1.3.3, company response to clarification question A21, and data on file.
NR, not reported.
[a] Number assessed at that specific timepoint for AADC-CU/1601 is based on data from Table 2 from Company clarification A10 (which is based on data on file generated to respond to the EAG clarification question).
[b] % calculated on basis of denominator as the number of patients at baseline, except for AADC-011. In AADC-011, two patients could not attend the 12-month follow-up due to COVID-19, so the denominator is N=10 instead of N=12.
[c] AADC-010 CSR Table 14.2.1.3.3
[d] Based on data from Table 14.2.1.1.3 of the AADC-011 tables and figures provided to the EAG at clarification questions.

[e] In AADC-011, not all subjects were able to return to the clinic for follow-up; as such, only 10 of the 12 enrolled subjects were assessed at Month 12. Subjects 011-311 and 011-313 were unable to return to the investigational site after Month 6 due to COVID-19 travel restrictions. At the Month 6 Visit, the highest motor milestone achieved by Subject 011-311 was standing with support (score of 2, mastery). Subject 011-313 had not achieved any motor milestones by the Month 6 Visit.".
[f] Based on data on file generated to support the Company response to clarification question A21.
[g] Results up to 60 months are reported in clarification response A21, but exact numbers of participants achieving each motor milestone at each timepoint is not reported.
[h] Based on data on file (T.NEW.MM) and as reported in EAG clarification A10

Table 3: AADC-010 - Summary statistics for time subjects experienced oculogyric crisis in hours per week following eladocagene exuparvovec treatment

Interval	Statistics	Observed Values	Change from baseline (Hours/Week)[a]
Baseline	n	[redacted]	-
	Mean (Std)	[redacted]	-
	Median	[redacted]	-
	Min, Max	[redacted]	-
Month 3	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 9	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Source: Final AADC-010 CSR (11 May 2022) Table 13
[a] No p-values reported
[b] 10 patients were enrolled in study AADC-010
Max: maximum; Min: minimum; Std: standard deviation

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15. PTC Therapeutics. *AADC-011 draft final clinical Study Report: A CLINICAL TRIAL FOR TREATMENT OF AROMATIC L-AMINO ACID DECARBOXYLASE (AADC) DEFICIENCY USING AAV2-HAADC - AN EXPANSION*. (2021).

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	PTC Therapeutics
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Manufacturer of eladocagene exuparvovec

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty whether all relevant data have been included in the CS (3.2.1.6 and 3.7) **EAG report ISSUE 1**	No	The Company believes that this issue can be resolved as all relevant data have been included in the Company submission. The Company submission is based on three clinical studies involving a total of 28 patients with severe AADC deficiency who received eladocagene exuparvovec: AADC-010, AADC-011, and AADC-CU/1601. While the EAG identified potential additional studies relevant to the appraisal, the studies identified by the EAG are not relevant to the appraisal. Further information on each non-relevant study is provided below: • **Studies conducted in Japan and reported in Kojima (2019):** The Company would like to clarify that the vector used in studies conducted in Japan (as reported in Kojima (2019)) is not the same as the vector used for eladocagene exuparvovec. It is a proprietary vector for which details are not available to the Company. As such, the Kojima (2019) study is not relevant to this appraisal. • **PTC-AADC-GT-002 (NCT04903288; N=2 at time of CS):** This open-label, single-arm study was designed to meet US Food and Drug Administration requirements for demonstrating the safety of the SmartFlow® cannula for delivery of eladocagene exuparvovec. The study primary outcome is adverse events associated with the SmartFlow® cannula and the key secondary outcome is change from baseline in F-DOPA PET uptake at the end of the trial phase (Week 8). Treatment in Study PTC-AADC-GT-

		002 commenced in July 2021 with an estimated primary completion date is July 2023. This study is not relevant to this appraisal because data are not yet available and because the study is focused on safety of the cannula with a very short duration. • **Patients in France treated under the Autorisation Temporaire d'Utilisation (ATU):** The EAG is correct that two patients with severe AADC deficiency have received eladocagene exuparvovec under an early access to medicines programme. At the time of the submission and Company SLR, the abstracts related to the two patients were not published. Descriptive results reported in the congress abstracts indicate that intraputaminal delivery of eladocagene exuparvovec was "safe and well-tolerated and resulted in significant improvements in motor and non-motor symptoms". Given that insufficient data were reported in the abstracts, and that the Company does not have further data beyond that described in the two congress abstracts (the congress abstracts were developed by the clinicians involved in treating the patients, with no involvement from the Company), data from the two patients could not be used in the appraisal. The EAG report also mentions AADC-1602. AADC-1602 is the long-term follow-up of beyond the trial period in patients enrolled in AADC-010, AADC-011, and AADC-CU/1601. The longer-term follow-up data from each study is already included in the Company submission including in the economic model. More information on patient enrolment in longer-term follow-up is provided in response to Issue 2.
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery (3.2.1.5, 3.2.5.1 and 3.7) **EAG report ISSUE 2**	Yes	The Company believes that this issue can be resolved by providing clarity around long-term follow up data collection, the procedure for progression to the longer-term follow-up, and data on the populations entering and not entering the long-term follow up. **Eligibility criteria and enrolment into long-term follow-up** The Company submission is based on three clinical studies (AADC-010 [N=10], AADC-011 [N=12], and AADC-CU/1601 [N=8]). The eligibility criteria for these studies are provided in Table 8, Table 9 and Table 10 of the CS, respectively. All patients from the parent studies were invited to enrol into the accompanying longer-term follow-up study (AADC-1602). There were no restrictions on eligibility for long-term follow-up and it has the following inclusion criteria: • The patient has a diagnosis of AADC deficiency

		• The patient was treated with eladocagene exuparvovec at the National Taiwan University Hospital. • The patient participated in the AADC-010, AADC-011, or AADC-CU/1601 studies. As with the parent studies, the National Taiwan University Hospital was the only study site for the longer-term follow-up. As of an ad hoc August 2022 analysis undertaken to support the response to this issue, among the total of 30 patients from the parent studies, [redacted] ([redacted]%) enrolled (as defined by signature of informed consent) in the longer-term follow-up. [redacted] ([redacted]%) from AADC-010 [redacted] and therefore did not sign informed consent and could not participate in the long-term follow-up study as they could not attend follow-up visits in Taiwan. Details on enrolment from each study are provided below. • **From AADC-010 (60-month study):** [redacted] patients enrolled into the longer-term follow-up, with [redacted] patient not enrolling due to [redacted]. The ad hoc August 2022 analysis indicates that [redacted] of the [redacted] patients enrolled into long-term follow-up currently contribute to the longer-term follow-up data. One patient who signed informed consent does not have data in the long-term follow-up because the patient died after their Month 12 visit due to influenza B, which was considered unrelated to eladocagene exuparvovec treatment. The longest timepoint of follow-up in AADC-010 is Month 84 ([redacted]) as of the August 2022 ad hoc analysis. • **From AADC-011 (12-month study):** [redacted] patients enrolled into longer-term follow-up. Of the [redacted] patients enrolled into longer-term follow-up, [redacted] currently have longer-term follow-up data. [redacted] patients do not yet have longer-term follow-up visit data, [redacted] of which were the patients impacted by COVID travel restrictions, and [redacted] had only just finished the parent study at the end of January 2022. All [redacted] of these patients are expected to attend longer-term follow-up visits in the future. The longest timepoint of follow-up from AADC-011 is 60 months ([redacted]) as of the August 2022 ad hoc analysis. • **AADC-CU/1601 (60-month study):** [redacted] patients enrolled into longer-term follow up. Of the [redacted] enrolled into longer-term follow-up, [redacted] patients have longer-term follow-up data. [redacted] who enrolled into long-term follow-up died (due to reasons unrelated to eladocagene exuparvovec treatment) before providing data in long-term follow-up. The

longest timepoint of clinical efficacy follow-up in AADC-CU/1601 is Month 120 ([redacted]) and for safety data is 144.9 months ([redacted]), as of the August 2022 ad hoc analysis.

It should be noted that the CEM is based on a February 2020 data cut (N=28) and not the ad hoc August 2022 analysis described above.

Baseline characteristics and motor milestone attainment in patients who did vs did not enrol in longer-term follow-up

As of the ad hoc August 2022 analysis to support the response to this issue, baseline characteristics (at the time of parent study initiation) are comparable between patients from AADC-010, AADC-011 and AADC-CU/1601 who enrolled into longer term follow-up ([redacted]) and those who did not enrol ([redacted]) (Table 1). Notably, the [redacted] from AADC-010 who did not enrol in long-term follow-up had achieved [redacted] (their last follow-up visit prior to [redacted] which indicates a very good response to eladocagene exuparvovec at that timepoint. The comparability in baseline characteristics and motor milestone achievement in patients who did versus did not enrol in long-term follow-up indicates that there is unlikely to be bias in the long-term follow-up data. It should be noted that whilst data in Table 1**Error! Reference source not found.** reflect the August 2022 ad hoc analysis (N=30), data in the CEM are based on a February 2020 data cut (N=28).

Table 1: Baseline characteristics in parent study of those who did vs did not enrol in long-term follow-up (N=30)

Characteristics	Category	Patients who enrolled in long-term follow-up by July 2022 (N=[redacted])	Patients who did not enroll in long-term follow-up by July 2022 (N=[redacted])
Age at baseline (months)	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]
Age at diagnosis (months)	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]

Baseline height, cm	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]
Baseline weight, kg	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]
Sex	Male	[redacted]	[redacted]
	Female	[redacted]	[redacted]
Race	Asian-Chinese	[redacted]	[redacted]
	Asian-Others	[redacted]	[redacted]
	Black	[redacted]	[redacted]
	White	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Genotype	Homozygous founder mutation	[redacted]	[redacted]
	Heterozygous founder mutation	[redacted]	[redacted]
PDMS-2 total score at baseline	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]
AIMS total score at baseline	Mean (SD)	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]

Abbreviations: AIMS - Alberta Infant Motor Scale; CM – Centimetres; PDMS-2 – Peabody Developmental Motor Scales 2nd Edition; kg – kilogram; max – Maximum; min – Minimum; SD – Standard deviation
Notes: Baseline refers to pre-initiation to parent study, not longer-term follow up.
Source: t_demo_adhoc [15 July 2022 data cut]

Long-term follow-up in the Company model

While the information above shows that there is no bias in the eligibility to participate in long-term follow-up, it should be noted that not all patients had longer-term data at the time of the February 2020 data cut used in the Company model. In the Company cost-effectiveness model:

		• **AADC-010:** None of the [redacted] patients enrolled in longer-term follow-up had data beyond the 60-month trial period, due to the timing of the data cut meaning patients had not yet reached the time of the first long-term follow-up visit. • **AADC-011**: [redacted] of the [redacted] patients enrolled in longer-term follow-up had data beyond the 12-month study period ([redacted] at Month 18, [redacted] at Month 24, [redacted] at Month 30, and [redacted] at Month 36) • **AADC-CU/1601**: [redacted] of the [redacted] patients enrolled in longer-term follow-up had data beyond the 60-month study period ([redacted] at Month 108).
It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived (3.2.6 and 4.2.6.1.1) **EAG report ISSUE 3**	Yes	The Company believes that this issue can be resolved by providing clarity on (i) the rationale to derive pooled estimate calculations, (ii) reasons for excluding two participants, and (iii) clarification of whether longer-term data from patients in AADC-011 are included in the model. **(i) Pooled estimate calculations for motor milestone achievement** As described in Issue 4, the Company would like to flag that all the options for modelling motor milestones based on the observed trial data are suboptimal and that it is much more appropriate to predict motor milestone attainment from PDMS-2 total score. Option 3 (using last observation carried forward [LOCF]; EAG base case), for example, is overly conservative and biased against eladocagene exuparvovec as it unrealistically assumes that patients cannot improve in motor milestone attainment beyond the point of their last follow-up. The LOCF approach for deriving motor milestone distribution is calculated by using the clinical trial data and carries a patient's last observation forward through to the five-year follow-up timepoint for those patients with less than five years of follow-up data. As can be seen in Table 2 below, at the time of the February 2020 data cut in the model, the number of patients providing data in the model diminishes over time as not all patients were treated with the gene therapy at the same time, meaning that those patients treated most recently will have shorter follow-up duration and therefore patient numbers in later timepoints decreases. For example, [redacted] ([redacted]%) patients do not provide data at Month 24, and [redacted] ([redacted]%) do not provide data at Month 36. Given that many patients continue to attain new motor milestones up to at least 5 years post-gene therapy, the LOCF approach prevents the model from capturing the continued improvement in motor milestone achievement that would be expected from patients with shorter follow-up. The LOCF method also carries forward the last observation for missed visits in

patients who have not dropped out but instead have just missed a follow-up visit. For example, in AADC-CU/1601 there was no Month 30 visit, so the Month 24 data are carried forward until the patient's next follow-up visit.

The predictive method (Company base case) is the only approach that allows future motor milestone attainment to be estimated in the model. In the predictive approach base case, future motor milestones can be attained up to 12 years, in line with the development of a normal child, which the EAG agreed was a "*duration [that] is consistent with that of a development of a healthy child".* This indicates that the EAG agrees that it is logical to assume that patients with shorter follow-up could attain future motor milestones. Further explanation of the limitations of the observed approach and the appropriateness of the predicted approach can be found in the Company's response to Issue 4.

The Company would like to highlight that the patient numbers and underlying calculations to derive the pooled estimates for the "percentage based on the original sample" approach (Option 1 of the observed distribution approaches described in response to Issue 4) and "patient distribution per follow-up" approach (Option 2 described in Issue 4) are already presented in the Company economic model ("Input Conversion" Sheet, B310:I320 of the file: ID3791 EE EAG model 22072022_ACIC). Further explanation of Option 1 and 2 is provided in the Company's response to Issue 4. Of note, please see Table 2 below for the number of patients at each timepoint, which highlights the limitations in all the observed data approaches due to the diminishing number of patients providing data in the model over time.

The Company therefore strongly believes that the predictive approach is the best and only plausible approach to modelling motor milestones as it mitigates this issue, allows future motor milestones to be attained, and uses more granular data from PDMS-2 scores rather than just discrete motor milestones.

Table 2: Number of patients providing data at each timepoint, N=28*

Time (months)	Patients with motor milestone data at each time point, % (N)
0 (Baseline)	[redacted]
12	[redacted]
18	[redacted]

		[redacted]

*Based on the February 2020 data cut used in the model. †Number of patients providing data in model is different to the number of patients assessed at each timepoint as some patients may not have been assessed at a given timepoint but were then assessed at a later timepoint (e.g. patients from AADC-CU/1601 were not assessed at Month 30 but were assessed at Month 36). **For the observed LOCF approach, motor milestones up to Month 60 only are used. Longer-term data are not used.*

(ii) Exclusion of two patients from AADC-011 due to COVID-19 travel restrictions

As stated in the CS and clarification responses, the primary endpoint analysis in AADC-011 is based on N=10 as opposed to the N=12 enrolled patients to reflect the 2 patients who could not attend follow-up due to COVID-19 travel restrictions. At the time of the CS and economic model data cut (Feb 2020), follow-up data for the 2 enrolled participants (Subjects 011-311 and 011-313) were not collected after Month 6, leading to insufficient data being recorded. This point was clarified in CS section B.2.6.2.2. ("Not all subjects were able to return for follow-up visits, primarily due to the COVID-19 pandemic)." It should be noted that both patients are expected to attend visits and provide data during the longer-term follow-up phase.

The two participants were not included in the observed distributions in the model (including the EAG base case [Option 3, the LOCF approach]) as the data were considered immature as of the February 2020 data cut used in the model. Including the patients would considerably bias the results against eladocagene exuparvovec given that patients require a longer timeframe than 6 months to demonstrate motor milestone improvements.

(iii) AADC-011 long term data

		The Company can confirm that longer-term follow-up data from beyond Month 12 of AADC-011 are included in the economic model. As of the February 2020 data cut used in the model, [redacted] of 10 patients had data beyond the 12-month study period in the model.
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies (3.2.6 and 3.7) **EAG report ISSUE 4**	Yes	The Company has responded to this issue in four parts, aligned to the EAG's request outlined in the EAG report. The four parts are as follows: (i) Clarification of extent of missing data and the extent imputed (ii) Rationale for predicting motor milestone attainment based on PDMS-2 total score (iii) Limitations of the approaches to calculate motor milestone attainment proportions based on the observed trial data (iv) Description of patients with fluctuations in PDMS-2 scores Please see below for a response to each part: **(i) Clarification of extent of missing data and the extent imputed** Please refer to the response to Issue 3 for details on how motor milestone attainment was determined in the model, and, for the LOCF approach (Option 3 described below), the extent of missing data/extent imputed given the heterogeneity in follow-up duration for patients in the model. **(ii) Rationale for predicting motor milestone attainment based on PDMS-2 total score** The Company strongly believes that the most appropriate approach to modelling motor milestones is by predicting motor milestone attainment based on PDMS-2 total score rather than using observed data from the clinical trials (i.e. the EAG's preferred base case). Predicting based on PDMS-2 total score is the most appropriate approach as it assumes that patients with limited follow-up data can achieve motor milestones in the future, whereas the observed data approaches do not allow for future motor milestone achievement. This is particularly pertinent when considering the clinical trial data during the observed trial timepoints, which show that many patients are on an upward trajectory in terms of PDMS-2 score and motor milestone attainment at the time of their last follow-up, and for some patients the upward

		trajectory is steep. It is therefore reasonable to assume that some of these patients would continue to improve in PDMS-2 scores and in turn attain motor milestones in the future (i.e. following their last follow-up), as is the case with the predicted approach using PDMS-2 total score. In line with this, the Company's approach assumes a 12-year period for the developmental phase, during which, with the predicted approach, patients are able to achieve motor milestones. The EAG agrees that 12 years is a "*duration [that] is consistent with that of a development of a healthy child*", supporting the rationale that it is reasonable to assume that patients with limited follow-up data may attain future motor skills (i.e. improvement in PDMS-2 total score) and in turn may accrue future motor milestones. This statement from the EAG contradicts their preference to use of the observed trial data LOCF approach and highlights that the predicted approach is more appropriate. **(iii) Limitations of the approaches to calculate motor milestone attainment proportions based on the observed trial data** As previously highlighted in the Company response to EAG clarification question B18, there were three options to estimating missing data when modelling motor milestones directly from the observed clinical trial data (i.e. these three options are in addition to the Company's preferred approach to predict motor milestones based on PDMS-2 total scores, which better reflects the full potential for child development and possibility for future motor function improvement): 1. **Percentage based on the original sample:** this option uses the observed clinical trial data but does not consider missing data. For example, at Month 60 N=[redacted] patients were assessed, of which N=[redacted] were in the sitting unassisted health state. The percentage based on the original sample approach uses N=[redacted] patients as the numerator and N=28 as the denominator, equating to a percentage of [redacted]%. By not considering missing data, the proportion of patients across the motor milestones does not sum to 100% for all timepoints after baseline, and patients with missing data are lost at the end of their follow-up. This option essentially means that patients die at the end of their follow-up, which is not a realistic nor plausible assumption. The number of patients evaluated at each timepoint in the model (as per the Feb 2020 data cut used in the cost-effectiveness model) can be found in **Error! Reference source not found.** in response to Issue 3 a bove.

		2. **Patient distribution per follow-up:** this option uses the observed clinical trial data, taking into account missing data and calculating the proportion of patients at each motor milestone using the total number of patients evaluated at that timepoint as the denominator value. Using the same example as above, in Option 2 the proportion of patients in the sitting unassisted health state at Month 60 is calculated as [redacted] patients out of the [redacted] patients being assessed at that timepoint (i.e. [redacted]%). By considering missing data, the proportion of patients in each motor milestone at each timepoint is the proportion of patients in that motor milestone out of the total number of patients with data at that timepoint. This means the percentages total 100% for all timepoints. 3. **The LOCF approach:** this option uses the observed clinical trial data and carries a patient's last observation forward through to the five-year follow-up timepoint for those patients with less than five years of follow-up data. The Company strongly believes that all of the approaches to model motor milestone attainment based on the observed trial data (and not using predictive models) are inappropriate as they all assume that future motor milestone attainment is not possible. The Company considers Option 1 to be inappropriate because it did not account for patients with missing data at the follow-up timepoints after baseline. This option therefore assumes that all patients exit the model at the end of their follow-up. This is reflected in the cost-effectiveness model analysis, as there is a loss of patients in the trace after baseline and the proportion lost continues to increase up until year 5, where it remains constant until the final cycle, with the exception of baseline mortality rate. This adds considerable bias and error to the model results and is not reflective of real-world practice. The Company considers Option 2 to also be inappropriate. Due to a low sample size of the trial population (N=28), using Option 2 would mean that each patient with data for the later timepoints carries a considerable amount of weight in the analysis. This is highlighted in **Error! Reference source not found.** in Issue 3 above, which shows that the number of patients with data at each timepoint declines over time: [redacted]% (N=[redacted]) of the original 28 patients have follow-up data at month 24, [redacted]% (N=[redacted]) patients at Month 36, [redacted]% (N=[redacted]) at Month 48, and [redacted]% (N=[redacted]) have follow-up data at month 60.

		Of the options to model motor milestone attainment based on observed trial data, Option 3 (LOCF approach; EAG base case) is more appropriate than Option 1 and 2 yet is less suitable than the predictive approach. Support for Option 3 is provided by the EAG's clinical expert, who advised the EAG (p68 of the EAG report) that "*due to eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time*", and FDOPA PET data in Tai et al (2022)[1] showing durable AADC enzyme activity up to 7 years. Despite this, Option 3 (LOCF approach; EAG base case) is not as appropriate as the predictive approach because it is overly conservative and biased against eladocagene exuparvovec as it unrealistically assumes that patients cannot improve in motor milestone attainment beyond the point of their last follow-up, which is clinically implausible. This is especially biased against patients with shorter follow-up (e.g. ≤24 months), as it does not account for the likely future motor milestone attainment that would happen if the patients were tracked over a longer timeframe. As shown in the clinical data, patients with longer follow-up data continuously improve in motor milestone achievement up to and beyond 5 years post-gene therapy. For example, one patient with 6 years of follow-up data demonstrates continuous motor improvement over the course of these 6 years, achieving the following: [redacted] Therefore, the LOCF approach for the observed distributions, as with all the observed data approaches, is unrealistic and biases the results against eladocagene exuparvovec. **(iv) Description of patients with fluctuations in PDMS-2 scores** On page 17 of the EAG report, the EAG point out that there are two patients in the eladocagene exuparvovec studies that experience a decline in motor scores at three- and five-years post-surgery, respectively. The EAG is correct that there were fluctuations in some patients' PDMS-2 total scores over time, which is to be expected given that PDMS-2 is sensitive to change. The Company would like to highlight that even though a patient may show a slight downward PDMS-2 total score trajectory, this does not mean that the patient's motor milestone achievement is affected, nor does it suggest a decline in the effect of eladocagene exuparvovec. For example, the apparent PDMS-2 total score declines in two patients in Figure 58 of the CS were due to

		external factors unrelated to gene therapy, and it should be noted that each patients' motor function remained above baseline despite the decline: • One patient (AADC-CU/1601 patient 1) had a left knee growth plate injury caused by infection that occurred before gene therapy. The left knee growth plate injury affected their ability to stand and walk, and therefore impacted their motor performance at follow-up. The patient experienced a gradual decline in motor scores 3 years after gene therapy. At 7 years, the patient underwent leg surgery and their motor function was stabilised thereafter. • One patient (AADC-CU/1601 patient 5) experienced a decline in PDMS-2 scores after 5 years. At 7 years, a panel of examinations confirmed that the AADC enzyme was fully functional in the patient, demonstrating durable gene replacement with eladocagene exuparvovec and highlighting that the PDMS-2 decline was unlikely due to loss of effect of eladocagene exuparvovec. It was found that the patient quickly became dystonic when undergoing training or examination, which likely explains the decline in PDMS-2 scores at follow-up timepoints. The patient received aquatic therapy, which stabilised their total PDMS-2 score decline.[1] [redacted]. This case study highlights that loss of motor function is not due to loss of AADC enzyme activity, but emphasises the importance of a holistic, multi-disciplinary approach (including sustained/consistent physical therapy as the patient grows and learns new skills) to ensuring optimal outcomes following treatment with eladocagene exuparvovec. In addition to the two patients with decline in PDMS-2 scores, the Company clarified in response to EAG question A21 that [redacted] in AADC-010 ([redacted]) had a fluctuation in motor milestone attainment in the longer-term follow-up, as per an ad hoc January 2022 analysis. [redacted] visit. At around Month 60 post-gene therapy, the patient experienced [redacted]. Therefore, between [redacted]

		[redacted] was [redacted] in motor function from [redacted], indicating a recovery from surgery. The [redacted] and further highlights that motor function fluctuations following eladocagene exuparvovec are usually due to external factors. Taken together, while there are fluctuations in PDMS-2 scores following treatment with eladocagene exuparvovec, the evidence indicates that fluctuations are not due to a reduction in the effect of eladocagene exuparvovec and do not mean a change in motor milestone attainment. Instead, fluctuations are driven by external factors (e.g. injuries, illness) and test fatigue (e.g. patient tiredness, and lack of cooperation, mood, and motivation) given the rigour and extensiveness of the PDMS-2 test. [redacted] [redacted] The importance of physical therapy in outcomes with eladocagene exuparvovec is to be expected given that patients are born with a deficit and miss out on key developmental milestones by the time they are treated. As stated above, the maximum motor function improvements after eladocagene exuparvovec are likely to be achieved through early diagnosis and treatment followed by holistic multi-disciplinary care and regular and continued physical therapy as the patient ages. In addition to the evidence showing that eladocagene exuparvovec's effect is likely to be sustained in the long-term, the EAG's clinical expert notes that "*they did not come across any patients showing a loss of skills or regression*" and that "*due to eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time*". As part of technical engagement, the Company consulted another clinical expert from Great Ormond Street Hospital (GOSH) with experience

		managing AADC deficiency, who agreed with the EAG's expert that the available evidence shows that eladocagene exuparvovec's effect is durable and that fluctuations in motor function following gene therapy are most likely due to external factors or test fatigue. Based on the above, to maximise and maintain treatment benefit and patient care following eladocagene exuparvovec, a multi-disciplinary approach to patient care is likely to be needed, including physical therapy (as captured in the resource use in the Company model).
Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5% (4.2.5 and 6.2) **EAG report ISSUE 5**	No	The Company strongly believes that eladocagene exuparvovec meets the criteria for the 1.5% discount rate and that the 1.5% rate was intended to cover situations similar to this, that is, when costs are incurred upfront, but benefits are accrued over a longer period. As per the NICE manual[3], the criteria for the 1.5% discount rate are as follows: 1) The technology is for people who would otherwise die or have a very severely impaired life. 2) It is likely to restore them to full or near-full health. 3) The benefits are likely to be sustained over a very long period. In summary of how eladocagene exuparvovec meets these criteria, clinical evidence shows that eladocagene exuparvovec can help to achieve truly transformative improvements in motor function, cognition, and other symptoms of AADC deficiency (e.g. oculogyric crisis) in patients, who go from not being able to control their own head or neck to being able to walk, talk and attend normal education within a few years of treatment (see videos in Tai et al 2022 and the video submitted to the EMA Scientific Advisory Group). This demonstrates the major impact on health and life outcomes for patients with AADC deficiency in terms of gaining independence and improved quality of life. The sustained treatment effect is supported by the underlying biology and mechanism of action of eladocagene exuparvovec, which shows sustained AADC enzyme activity up to at least 7 years post-gene therapy. Validation of the clinical data is provided by the EAG's clinical expert, who explained that the underlying mechanism of eladocagene exuparvovec means that patients should maintain motor function improvements over time, and carers of patients with AADC deficiency (taken from the patient organisation submissions), who note the miraculous impact of eladocagene exuparvovec. In addition, another GOSH clinical expert consulted by the Company during technical engagement agreed with the

		EAG's expert that the effect of eladocagene exuparvovec should persist over the longer-term and that gene replacement is durable when administered to non-dividing cells in the brain. Taken together, there is clear evidence that eladocagene exuparvovec meets all the criteria for the 1.5% discount rate and is consistent with other appraisals where the lower discount rate has been accepted by NICE. The detailed justification on how eladocagene exuparvovec meets the criteria for a 1.5% discount rate is described as follows: **1) Eladocagene exuparvovec is for people who would otherwise die or have a very severely impaired life** AADC deficiency is an ultra-rare, fatal, genetic disorder, with onset from birth and a wide range of severe symptoms. In severe cases, patients spend their shortened lifetime with little or no motor function and are likely to die before their twenties.[4–6] In fact, the patient-level Natural History Database[7] developed by the Company and a natural history study by Hwu *et al.* 2012[4] shows that patients who die typically do so in childhood. Severe AADC deficiency significantly impacts patients from birth onwards, affecting major aspects of their development, motor skills, growth, cognitive and language skills, and behaviour.[8–10] The most common characteristic of severe AADC deficiency is lack of motor development, with natural history studies indicating that over 95% of patients fail to achieve any motor milestones typically associated with child development[10] (e.g. head control, sitting unassisted, standing with support, and walking with assistance) during their lifetime, despite the use of best supportive care and symptomatic treatments. In addition to failing to develop, patients with AADC deficiency suffer a range of neurologic and cognitive impairments, including hypotonia (low muscle tone/floppiness), movement disorders including dystonia (involuntary muscle contractions), hypokinesia (smaller than expected movements), and regular seizure-like episodes of oculogyric crises [OGC], jaw spasms, hyperextension of the head/neck/back, and involuntary contractions.[11] Patients also experience excessive crying, sleeping problems, irritability, problems with digestion, cognitive impairment, developmental delay, and autonomic symptoms.[8,11] They require round-the-clock care for their whole lives. The severe and debilitating nature of AADC deficiency is highlighted in videos in Tai *et al.* (2022)[1] and in the video submitted to the EMA Scientific Advisory Group. The Company

		strongly encourages the EAG and Committee to review these videos and has provided them as part of the reference pack associated with this technical engagement response. Prior to eladocagene exuparvovec, there were no approved disease-modifying therapies in AADC deficiency and symptomatic treatments have very limited effect. The majority of severe patients therefore face a shortened lifetime of very severe health deficits with little hope of improvement, which not only impacts the patients but also their family caregivers. Taken together, it is clear that eladocagene exuparvovec is for people who have a severely impaired life and who would otherwise die. **2) Eladocagene exuparvovec is likely to restore patients to near-full health** The Company would like to note that the "full or near-full health" criteria is ambiguous as it does not consider or define what "full or near-full health" is relative to each condition. The GOSH clinical expert consulted by the Company as part of technical engagement stated that full health/typical development is not likely to be possible in patients with AADC deficiency. This is because patients experience severe and wide-ranging developmental deficits from birth and potentially even in utero (as explained by (i) the GOSH clinical expert, (ii) the fact that patients with AADC deficiency present as early as 3 months of age, (iii) the non-viability of AADC knockout mice, and (iv) the in utero problems in mice engineered to have a significant decrease in AADC production[12]), and therefore start life from a baseline that is very far from what may be considered as "full or near-full health". In fact, the developmental deficit in patients with AADC deficiency may be too large to be able to restore patients to "full or near-full health" by the time the patient is diagnosed or is eligible to receive eladocagene exuparvovec. Limited insights on defining "near-full health" can be gathered by comparing to proxy diseases as very few conditions truly reflect the broad-ranging, immediate-onset, and severity of the impacts of AADC deficiency. Therefore, the Company encourages further consideration by the Committee to determine how it is appropriate to define "full or near-full health" in the context of AADC deficiency and this appraisal. Despite the inherent challenges of meeting this criterion in AADC deficiency, some patients with AADC deficiency have shown transformative benefits within several years of receiving eladocagene exuparvovec and may be considered to have returned to "near-full health". From a baseline of no motor function and severe cognitive and language impairment, some patients

		can walk, talk, run, play, socialise with other children, and attend standard school within a few years of treatment with eladocagene exuparvovec. The improvements are rapid (as early as 3 months) and are observed across all the symptoms measured in patients with AADC deficiency (e.g. autonomic symptoms, OGC frequency/duration). The transformative and health-restoring benefits of eladocagene exuparvovec are best illustrated in a video provided in Tai *et al.,* (2022)[13] and in a video provided by PTC as part of the EMA Scientific Advisory Group meeting[14]. Tai et al. (2022) describes [redacted] patients aged [redacted] at baseline, respectively, who could walk freely without assistance just [redacted] after receiving eladocagene exuparvovec (one of which is in the video clips in the paper), while a separate patient in the EMA Scientific Advisory Group video could walk, run, and talk [redacted] of treatment – a similar timeframe to a healthy child from birth. These life-changing improvements are truly remarkable and demonstrate that a proportion of patients receiving eladocagene exuparvovec are restored to "near-full health", particularly taking into account the developmental deficit at the point of treatment with eladocagene exuparvovec. The timeframe of improvement in their development from the time of gene therapy is similar to that of a normal child from birth (i.e. within 2 years of treatment, a patient can achieve similar levels of motor and cognitive function as a healthy 2-year old achieves from birth). This may be considered "near-full health", and it may even be argued that their improvement is above what could conceivably be expected given that most patients do not attain any motor milestones without gene therapy and given the wide-ranging and severe developmental deficits experienced by the patient up the point of treatment (i.e. the patient may have missed out on key opportunities to develop between birth and treatment, when their brain has high neuroplasticity and is undergoing critical development). Further support for the life-changing effect of eladocagene exuparvovec is provided in carer testimonials provided to the EAG for this appraisal. One parent explained that since gene therapy *"every day has been a miracle"* and explained that there is "*a* '*metamorphosis' following gene therapy in which his 'almost paraplegic' child became a 'happy girl that's running around'*". Another mother explained that gene therapy has "*solved"* her child's symptoms and described this as "*a miracle*". She explains that "*his 'mood has changed', that beforehand he was 'always angry, always crying' but has since been more interactive and is no longer afraid of other children*

		but laughs with and tries to communicate with them". The patient and caregiver benefits of the gene therapy are therefore considerable. Despite the evidence above, the Company acknowledges that even though eladocagene exuparvovec has shown transformative benefits in some patients with AADC deficiency, there are limitations with the maximum achievable benefit. For example, eladocagene exuparvovec does not increase serotonin production, which is to be expected because serotonin is predominantly produced in the midbrain whereas eladocagene exuparvovec is administered in a different area of the brain (putamen). In addition, the maximum achievable benefit with eladocagene exuparvovec is reliant on a continuous, holistic approach to patient care, including early diagnosis and administration of gene therapy, followed by multi-disciplinary treatment and continuous physical therapy. The maximum effect is likely to involve healthcare professionals across a range of disciplines including physiotherapy, speech therapy, dieticians, paediatricians, and also includes symptomatic therapies (as reflected in the Company economic model). Treatment success may also be dependent on the level of support from family caregivers in ensuring patients remain motivated and continue to practice physical therapy (as noted in Issue 4). **3) The benefits of eladocagene exuparvovec are sustained over a very long period** Eladocagene exuparvovec has a durable effect and current biologic, clinical, and expert evidence highlights that its benefits are likely to be sustained in the very long-term. From a biologic perspective, eladocagene exuparvovec corrects the underlying cause of AADC deficiency by replacing the non-functioning *DDC* gene. It is a recombinant adeno-associated virus 2 (rAAV2) vector, which, as highlighted by the EMA, "*was chosen as the vector for delivery due to its demonstrated long-term gene expression in the CNS, and the extensive testing of this serotype in nonclinical species and humans, including patients with Parkinson's disease, where AADC activity, dopamine induction, and motor function improvement and safety were demonstrated. In addition, rAAV2 has shown long-term gene expression in vivo, which offers a treatment for genetic diseases affecting the nervous system.".* In a Parkinson's disease monkey model,[15] behavioural recovery was sustained up to at least 15 years after administration of an rAAV-based gene therapy to the putamen. The site of administration (putamen) is critical to the durability of eladocagene exuparvovec – the brain contains non-dividing cells, and the rate of

		cell turnover is a key determinant in gene therapy stability. Based on this, eladocagene exuparvovec is expected to durably replace the non-functioning *DDC* gene and therefore durably lead to AADC enzyme activity. This is validated by the Company's Response to EAG clarification question B6, which explained that AADC enzyme activity has been shown to be sustained at [redacted]- and even [redacted]-years follow-up following treatment with eladocagene exuparvovec, as evidenced by neuroimaging. It is further validated by the GOSH clinical expert consulted by the Company, who confirmed that gene replacement is durable when administered into the brain. In addition to the biologic evidence, clinical evidence demonstrates the sustained benefits that eladocagene exuparvovec brings to patients, with Company response to EAG clarification A21 highlighting that eladocagene exuparvovec provides sustained clinical benefits up to 10 years. Clinical expert comments in the EAG report support the persistence of eladocagene exuparvovec's sustained benefits: "*Clinical advice to the EAG is that, due to eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time.*" (Page 67 of EAG report). The GOSH clinical expert consulted by the Company agreed with the EAG's expert that the mechanism of action and evidence so far indicates that the treatment effect of eladocagene exuparvovec should persist in the long-term. In addition to highlighting that eladocagene exuparvovec meets the criteria for a 1.5% discount rate, the Company would like to raise the following: • **The case for eladocagene exuparvovec meeting the 1.5% discount rate criteria is analogous to other NICE appraisals where the 1.5% discount rate was accepted** The Company considers this appraisal to be similar to HST15 (onasemnogene abeparvovec)[16], which is for a one-time gene therapy administered for treating spinal muscular atrophy in a severely disabled paediatric population with motor impairments. In HST15[16], NICE accepted a 1.5% discount rate and the committee "*acknowledged that onasemnogene abeparvovec has a high one-off cost, whereas the benefits are accrued over the lifetime of the patient*". The committee also considered that "*it was likely that the alternative 1.5% discounting rate was intended to cover situations similar to this (that is, when costs are incurred upfront, but benefits are accrued over a longer period)*" and "*acknowledged that the technology was transformative*

		for people who, without treatment, would otherwise die". Additionally, the committee "*was uncertain about whether most people who have onasemnogene abeparvovec would be considered to have 'normal or near-normal health' but believed a proportion might*". These considerations from HST15[16] are all relevant to eladocagene exuparvovec for patients with AADC deficiency – eladocagene exuparvovec has a high one-off cost but benefits are accrued over the lifetime of the patient, it is transformative for people who would otherwise live a very severely impaired life and die, and the evidence shows that a proportion of patients have normal or near-normal health following treatment, particularly those treated at an early age. The Company would also like to note that eladocagene exuparvovec has up to 10 years of follow-up data for some patients, which is extremely rare for a therapy at the time of regulatory approval and is a considerable strength of the eladocagene exuparvovec evidence base. Other therapies have had a 1.5% discount rate accepted based on follow-up data for shorter durations, including TA538 (dinutuximab beta for treating neuroblastoma; maximum follow-up of 5-years)[17] and TA235 (mifamurtide for the treatment of osteosarcoma; follow-up of 7.9 years)[18]. While the Company acknowledges that these examples are not HSTs, and that longer follow-up data is always desirable for all appraisals, we believe that the 10-year data is a strength of this submission and sufficient to meet the criteria for the 1.5% discount rate. • **Eladocagene exuparvovec meets the UK Treasury Green Book definition for a 1.5% discount rate** The Company would also like to note that the UK Treasury Green Book states that "a reduced rate of 1.5% per annum applies to policies that impact health or life outcomes".[19] While the Company is aware that this was a point of focus in NICE's methods review and the final decision was to continue with the 3.5% rate for NICE appraisals, it is worth noting that the UK Treasury Green Book's rate of 1.5% per annum should technically apply to the appraisal of eladocagene exuparvovec. Taken together, there is evidence that eladocagene exuparvovec meets all the criteria for the 1.5% discount rate and is consistent with other appraisals where the lower discount rate has been applied.

Use of PDMS-2 scores to predict motor milestone achievement (4.2.6.1.1 and 6.2) **EAG report ISSUE 6**	No	The Company strongly believes that using PDMS-2 total scores to predict motor milestones in the CEA is preferable to using the observed trial motor milestone achievements. The reasons for it being more appropriate can broadly be grouped as follows: (i) Predicting motor milestones based on PDMS-2 allows for future motor milestone attainment over the full developmental phase of a child, while making the most out of the available trial data. (ii) PDMS-2 is a rigorous and well-validated measure of motor function that is sensitive to change. (iii) PDMS-2 scores provide a more complete picture of the effect of eladocagene exuparvovec (including providing data on fine motor function) than motor milestone attainment alone. More information on each reason is provided below: **(i) <u>Predicting motor milestones based on PDMS-2 allows for future motor milestone attainment over the full developmental phase of a child, while making the most out of the available trial data.</u>** As noted in response to Issue 4, the Company strongly believes that the most appropriate approach to modelling motor milestone attainment is by predicting based on PDMS-2 total score. As described in the CS (Section B.3.3.1.1.1), the cost-effectiveness model for this submission uses established statistical models to predict motor milestone achievement based on observed trial PDMS-2 total score data for individual patients. This approach overcomes challenges with the small sample size, heterogeneous patient trajectories, and different lengths of follow-up data for some patients (e.g. some patients treated with eladocagene exuparvovec in AADC-011 have only 12 months of follow-up data, whereas some patients from AADC-CU/1601 have at least 9 years of follow-up data in the model). Modelling motor milestone attainment using predictive models allows for the modelling of PDMS-2 scores over time instead of at explicit timepoints. Therefore, while there may be small fluctuations in the PDMS-2 scores, the fitted model (Gompertz in the Company base case) reflects the overall trend in the PDMS-2 trajectories. The Company notes that the EAG report states the Company's predicted distributions lead to higher proportions of patients in the best health state and lower proportions in the worst health

		state than using the observed trial data alone. This is not because the predicted approach overestimates the treatment effect at each timepoint, but is because the predicted approach has accounted for future motor milestone attainment in patients with less follow-up time, whereas the observed approach has not. It is therefore inappropriate to make a direct comparison between the observed and predicted distributions. **(ii) <u>PDMS-2 is a rigorous and well-validated measure of motor function (including providing data on fine motor function) that is sensitive to change</u>** PDMS-2 is appropriate for predicting motor milestone achievement as it is a validated, rigorous and reliable measure of gross and fine motor function and incorporates quantitative and qualitative rating criteria that is proven as a reliable tool to monitor progress and change in motor skill development and acquisition over time.[20] Using specific items to define motor milestone achievement allows for reproducible, objective data that may be more reproducible and objective than clinician judgement. PDMS-2 was used in AADC deficiency specifically in a natural history study of 37 patients in Taiwan (as noted in CS Section B.3.2.2.7), giving benchmark values in patients treated with best supportive care and demonstrating that it can be used in AADC deficiency patients specifically.[10] While the Company acknowledges that PDMS-2 is not routinely used in UK practice, in the context of a clinical trial, PDMS-2 is a rigorous tool and may give a more reliable and sensitive measure of motor function than clinician judgement alone. In a 2018 comparison of instruments to measure child gross motor function, PDMS-2 was noted as having excellent test-retest reliability and was stated as being among the most reliable assessments for gross motor function in children.[21] The Company notes that the EAG report (page 18-19) states that "*motor milestone achievement states are more reflective of how motor function is assessed in practice than the PDMS-2 scores*". While this may be a fair comment, the Company would like to reiterate that key motor milestones in the clinical trials for eladocagene exuparvovec are determined based on items of the PDMS-2 scale, and the EAG clinical expert confirmed that the trials determined motor milestone achievement appropriately. As noted in point (iii) below, PDMS-2 provides a comprehensive assessment of gross and fine motor skills, so can also capture meaningful patient improvements that aren't necessarily reflected in the discrete motor milestones.

		In addition, as noted in the CS Section B.3.2.2.7, the use of PDMS-2 was accepted by NICE as an appropriate instrument to measure motor function in studies that informed the NICE clinical guideline on the diagnosis and management of cerebral palsy (CP), and was shown to have good test-retest reliability, responsiveness, and sensitivity to change in a study exploring its validity in CP.[20,22] PDMS-2 has also been validated in various populations across various geographies[22], and is considered a reliable tool used in several countries.[22] **(iii) <u>PDMS-2 scores provide a more complete picture of the effect of eladocagene exuparvovec than motor milestone attainment alone</u>** The PDMS-2 test is a comprehensive assessment of motor function and is able to capture slight differences in motor development over time due to the scope of questions tested. The PDMS-2 test is fully comprehensive and tests across 6 subscales/areas of motor development: reflexes (8 items), stationary (30 items), locomotion (89 items), object manipulation (24 items), grasping (26 items), visual motor integration (72 items). Within the Company's economic model, PDMS-2 total scores are used within a growth model to predict motor milestone achievement during the 12-year development phase. By capturing data in addition to key motor milestones, PDMS-2 can provide a more complete picture of a patient's motor function than just assessing motor milestone achievement alone. As well as the PDMS-2 scale giving a more reliable and sensitive measure of motor function than "clinician judgement", the 2018 comparison of tools to measure gross motor function in children[21] (mentioned above) also states that PDMS-2 is the only measure that is sensitive to *partial* mastery of a task and one of only four tools with a reported minimum clinically important difference (MCID) with satisfactory sensitivity and specificity.[21] This is particularly pertinent as the EAG report Section 3.2.3.1 states that "*our expert also thought it reasonable and clinically relevant to consider both 'newly emerging' skills and 'mastery' of key motor milestones*."
Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes (4.2.6.3, 6.1 and 6.2) **EAG report ISSUE 7**	No	The Company strongly believes that the persistence of treatment benefit in the long-term, over a patient's lifetime, is supported by the clinical evidence and underlying biology and mechanism of action of eladocagene exuparvovec. There are three key points to consider: (i) Eladocagene exuparvovec durably restores AADC enzyme functioning.

		(ii) The eladocagene exuparvovec clinical trials have demonstrated sustained improvement in motor milestone achievement throughout follow-up. (iii) The Company considers the EAG's treatment waning scenario to be unrealistic. More information on each point is provided below: **(i) Eladocagene exuparvovec durably restores AADC enzyme functioning** As noted in response to Issue 5, eladocagene exuparvovec corrects the underlying cause of AADC deficiency by replacing the non-functioning *DDC* gene. The EMA note that rAAV2 was chosen as the vector for delivery due to its demonstrated long-term gene expression in the CNS.[23] The EMA also note that the eladocagene exuparvovec vector "*has the ability to confer long-term stable gene expression without associated inflammation or toxicity*."[23] Of importance is the target site of gene therapy administration (neurons in the putamen region of the brain) – neurons are non-dividing cells, meaning gene replacement is stable for as long as the neurons are intact. This is supported by Parkinson's disease primate models showing gene transduction up to 15 years following gene therapy administration.[15] In line with stable gene replacement and as stated in Company Response B6 in the EAG clarification questions, AADC enzyme activity is sustained at up to 7 years follow-up, as indicated by FDOPA PET uptake increases from baseline following eladocagene exuparvovec treatment (Figure 2 in Tai *et al*., 2021[1] and Table 18, Table 24, Figure 37 in CS). Therefore, given the technology's mechanism of action and the evidence of sustained AADC enzyme activity, there is no evidence to conclude that a waning of the treatment effect would occur from a biologic and mechanism of action perspective. In line with this, the EAG's clinical expert commented in the EAG report: "*Clinical advice to the EAG is that due to eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time*" (Page 67 of EAG report). Likewise, the GOSH clinical expert consulted by the Company as part of technical engagement stated that eladocagene exuparvovec's effect should be durable based on its mechanism of action, site of administration, and the clinical evidence so far.

		(ii) The eladocagene exuparvovec clinical trials have demonstrated sustained improvement in motor milestone achievement throughout follow-up As noted in response to Issue 5, evidence in patients treated with eladocagene exuparvovec indicates that patients improve and retain motor function in the long-term. As presented in Tai *et al.,* 2021[13], Figure 4, all patients had an improvement from baseline in PDMS-2 total scores following eladocagene exuparvovec and the effect was sustained throughout the follow-up duration. At baseline, patients had a very low mean PDMS-2 score of [redacted] ([redacted]), which increased rapidly to [redacted] ([redacted]) at 1 year, [redacted] ([redacted]) at 2 years, and [redacted] ([redacted]) at 5 years. All patients treated with eladocagene exuparvovec, including those with follow-up beyond 5 years, have higher PDMS-2 total scores than at baseline, demonstrating the long-term motor function improvement with eladocagene exuparvovec. Notably, and in line with the clinical data showing sustained treatment benefit, the EMA concluded that it is not appropriate to assume a decline of treatment effect of eladocagene exuparvovec over time: "[redacted]". While the clinical effect is expected to be sustained in the long-term, the Company acknowledges that Figure 58 in the Company submission suggests that there is at least one patient with a downward PDMS-2 trajectory. As discussed in response to Issue 4, the fluctuations in PDMS-2 total scores is unrelated to eladocagene exuparvovec and is more likely due to external factors (e.g. injury), test fatigue, and/or lack of physical therapy.[1] Notably, the EAG's clinical expert notes that "*they did not come across any patients showing a loss of skills or regression*" and that "*due to eladocagene exuparvovec's mechanism (continued production of the AADC enzyme), it is likely that people will maintain improvements in their motor function over time*". The GOSH clinical expert consulted by the Company during technical engagement agreed with the EAG expert. Therefore, the Company does not consider it relevant or appropriate to consider a treatment waning scenario within the model. **(iii) The Company considers the EAG's treatment waning scenario to be unrealistic**

		The EAG included a pessimistic and exploratory treatment waning scenario in their updated economic model, which was derived from an exploratory analysis in HST15 (onasemnogene abeparvovec for treating spinal muscular atrophy). The scenario assumes that patients regress from higher to lower functioning health states after 25 years of treatment. It should be noted that this scenario was not included as the NICE Committee's preferred assumptions in HST15. In addition, while a useful analogue, it should be noted that onasemnogene abeparvovec differs to eladocagene exuparvovec in its target cell and route of administration – onasemnogene aberpavovec is administered intravenously into the blood and passes into the nerves, whereas eladocagene exuparvovec is administered directly into the putamen into neuronal cells. The target cell and rate of cell turnover is important in gene therapy durability.[15] Given the biologic evidence showing stable *DDC* gene expression and no waning of AADC enzyme activity over time, along with the clinical evidence and EAG expert comments showing that patients should maintain motor function over time, it is implausible to assume that the effect of eladocagene exuparvovec would wane over time and the Company strongly believes that a waning scenario is unrealistic. In line with this, the Company is not aware of any evidence to date that shows a waning effect for gene therapies administered to the cells of the nervous system (including the brain). This was confirmed by the GOSH clinical expert consulted by the Company during technical engagement.
The survival extrapolation methods used by the company overestimate survival (4.2.6.2 and 6.2) **EAG report ISSUE 8**	No	The Company accepts that this issue can be resolved. The Company accepts the EAG's proposed use of the Weibull parametric curve for the following four health states in their base case: no-motor function, full head control, sitting unassisted, and standing with support. The Company originally selected the log-logistic curves for the no-motor function, full head control, sitting unassisted, and standing with support health states as the base case as it provided conservative survival estimates for patients with AADC deficiency. However, the Company agrees that the Weibull parametric curves provide a more accurate estimation than the Company base case when compared to the observed survival estimates derived from Brooks *et al.* (2014) for the 10-year, 20-year and 30-year timepoints.[24]

		The Company and EAG both agree that the exponential parametric curve is preferred for the base case for the walking with assistance health state. This is due to the intersection of the walking with assistance survival curve and the standing with support survival curve beyond 45 years if the Weibull parametric curve was used for all health states (which is deemed implausible given that two UK clinical experts consulted by the Company prior to submission agreed that an improvement in motor milestones would likely correspond to an improvement in survival, with one expert explaining that attainment of motor milestones may reduce the risk of secondary complications associated with AADC deficiency). The impact of the changes of the survival curves approach on the Company's base case ICER is small and can be found in the 'Summary of changes to the company's cost-effectiveness estimate(s)' Section of this document. **Discrepancy in Table 27, EAG report** While the Company accepts the EAG's preferred survival curves, we would like to highlight a discrepancy in Table 27 of the EAG report regarding the EAG's interpretation of the Company's survival estimates for patients in the "no motor function" health state. The EAG has stated that the Company's predicted approach underestimates survival in the no motor function health state. The EAG determined this based on a comparison of survival estimates from cerebral palsy (CP) patients in the "Does not lift head in the prone position" health state with *a weighted average of CP patients who are tube-fed, fed orally by others, and self-fed* from Brooks *et al.* (2014).[24] The Company agrees that most appropriate CP patients to map to AADC deficiency no motor function are those in the "Does not lift head in the prone position" but would like to clarify that our model survival estimates for this health state are based on those CP patients who are *tube-fed only* (rather than a weighted average of all the feeding types). Please see below for a comparison between the Company approach and the EAG approach to mapping survival data from CP patients to the no-motor function health state: • **In the Company's model:** the no motor function health state in AADC deficiency is assumed to be equivalent to *CP patients who are tube-fed only* in the 'Does not lift head in the prone position' health state in Brooks *et al.* (2014). • **In the EAG's report:** the no motor function health state in AADC deficiency is assumed to be equivalent to *a weighted average of CP patients who are tube fed, fed orally by*

others, and self-fed in the 'Does not lift head in the prone position' health state in Brooks *et al.* (2014).

Table 3 provides a comparison of the Company's predicted survival for AADC deficiency patients in the no motor function health state (using the Weibull distribution) vs survival based on Brooks *et al.* (2014) CP patients in the "Does not lift head in the prone position" for *tube-fed only* vs Brooks *et al.* (2014) CP patients in the "Does not lift head in the prone position" for a *weighted average of tube fed, fed orally by others, and self-fed*. When comparing the Company's predicted survival for AADC deficiency patients to "tube-fed only", the survival estimates are similar.

The Company strongly considers *tube-fed only* to be more appropriate than a weighted average of feeding types for AADC deficiency patients in the no motor function health state. Many patients with severe AADC deficiency are tube-fed throughout their lifetime, as supported by the GOSH clinical expert consulted by the Company during technical engagement, who confirmed that this assumption is accurate as patients with severe AADC deficiency with no motor function are gastronomy-fed. Moreover, as noted by a UK clinical expert consulted by the Company as part of this appraisal, <10% of AADC deficiency patients with no motor function live into their twenties and the EAG's clinical expert noted that mortality risk increases in adolescence, which together suggest that the EAG's value of 51% of patients living to 20 years is likely to be an overestimate and the Company's predicted survival of 35% is likely to be more reflective of survival in AADC deficiency patients with no motor function.

Table 3: Observed and predicted survival estimates for patients with AADC deficiency in the no motor function health state as stated in the Company's revised base-case (i.e. following technical engagement and the EAG report)

Timepoint	Company model values: Predicted survival for patients with AADC deficiency in the no motor function health state[a]	Survival in CP patients in the "does not lift head in the prone position" from Brooks *et al.* (2014)[a]	
		Tube-fed only[b] (used by the Company	Weighted average across tube fed, fed orally by others, and self-fed[b,c]
10 years	68%	75%	81%
20 years	35%	41%	51%

		<table><tr><td>**30 years**</td><td>15%</td><td>26%</td><td>36%</td></tr><tr><td>**50 years**</td><td>2%</td><td>NR</td><td>NR</td></tr></table> Survival estimates presented for the no motor function health state only [a]Based on the Weibull distribution [b]Values used by the Company to map to AADC deficiency patients in the no-motor function health state [c]Values states in Table 27 of the EAG report and assumed by the EAG to be reflective of AADC deficiency patients in the no motor function health state
It is unclear how reflective the company's resource use estimates are of clinical practice (4.2.8 and 6.2) **EAG report ISSUE 9**	No	The Company believes that this issue can be resolved by agreeing to the changes proposed by and discussed with the EAG. The updated base case reflecting these changes is provided in the following section: Summary of changes to the company's cost-effectiveness estimate(s). Please see below for further detail on the changes made to the base case to incorporate the EAG clinical expert's recommendations: **Pre-operative resource use:** • **MRA, lumbar puncture, and FDOPA PET scans**: In the original submission, the Company did not include MRA, lumbar puncture, or FDOPA PET scans in the pre-operative resource use costs. The EAG have since consulted with a clinical expert and suggested that patients have an MRA scan prior to surgery, a CSF lumbar puncture to measure baseline serotonin and dopamine metabolites, and a FDOPA PET scan to measure baseline AADC enzyme activity. The Company accept this update and have included these additional resource use costs in the base case, as shown in Table 4. **Post-operative resource use:** • **Cost per stay vs cost per day:** At the technical engagement teleconference for this appraisal, held on 18th August 2022, the EAG confirmed that the Company's approach to assuming that the that costs sourced from the National Schedule of Reference Costs for a paediatric intensive care unit (ICU) stay and paediatric ward stay are *per stay*, as per the Company's original base case, rather than *per day*, as the EAG had applied in their preferred base case reported in the EAG report. The Company and the EAG therefore agree that cost *per stay* should be applied as shown in Table 4.

- **ICU cost code:** Previously, the Company had costed the ICU stay under code XB01Z (CCU04; Paediatric intensive care unit: paediatric critical care patients predominate, advanced Critical Care 3) at £3,305.99. The Company agree with the EAG's proposed update for the ICU per stay code of XB01Z (CCU04; Paediatric intensive care unit: paediatric critical care patients predominate, advanced Critical Care 5) at £7,866.03 (as also discussed in the technical engagement teleconference on 18th August 2022). The company accept this update to the base case as shown in Table 4.
- **CT, PET, and FDOPA scans:** The Company originally included three CT scans and two PET scans as post-operative resource use frequencies in the base case. The EAG's clinical expert advised that patients do not have any CT scans in the post-operative phase. The clinical expert also advised that patients do not have any post-operative PET scans; instead, two FDOPA PET scans (more expensive than a PET scan) are conducted to compare AADC enzyme activity, one pre- and one post-operation. The Company accept this update to the base case as shown in Table 4.

Table 4: Revised Company base case: Pre- and post-operative resource use and costs associated with administration of eladocagene exuparvovec

Resource use	Frequency assumed by company	Frequencies based on EAG's clinical opinion	The Company's accepted new base case
Pre-operative resource use			
MRI scan	2	2	2
MRA	0	1	1
Lumbar puncture	0	1	1
FDOPA PET scan	0	1	1
Post-operative resource use			
Paediatric intensive care unit (per stay)	1	at least 2 days	1
Paediatric ward stay (per stay)	1	Between 5-7 days	1

Multidisciplinary team follow-up visits post-surgery	8	8 (2-3 times in the 1st month and thereafter at least 5-6 visits in the 1st year)	8
CT scan	3	0	0
PET scan	2	0	0
FDOPA-PET scan	0	1	1
Lumbar puncture	1	1	1

Proportion of patients treated with best supportive care per motor milestone health state:

The Company used AADC deficiency consensus guidelines[8] to inform the treatment doses in the best supportive care basket. Compared to the Company's inputs, the EAG's clinical expert felt that:

- All patients in UK practice are likely to receive dopamine agonists and vitamin B6.
- Clonidine is not used in the UK.
- More patients in UK practice are expected to receive benzodiazepines and melatonin
- Approximately a quarter of patients in UK practice would need anticholinergic agents.
- L-DOPA is not used in UK practice.
- Patients in the UK are given folinic acid, not folic acid.
- Patients in the UK receive dietary supplements and vitamin D (including 100% receiving vitamin D).

The Company accepts all of the suggested changes by the EAG's clinical expert (Table 5).

Table 5: Revised Company base case: Proportions of patients treated with each treatment category in the best supportive care basket per motor milestone state (based on EAG expert advice)

	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Dopamine agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		[redacted]

MAO inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin B6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benzodiazepines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Melatonin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clonidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L-Dopa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Folinic acid (vitamin B9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dietary supplement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: this is an adjusted version of CS Table 57, but with proportions adjusted to reflect clinical advice received by the EAG.

Annual number of follow-up visits, hospitalisation, and A&E attendance per motor milestone health state:

The EAG's clinical expert largely agreed with the Company's assumptions for resource use, apart from the following:

- Patients in UK practice are likely to have one to two dietician appointments per year and 2 to 3 appointments with a nurse in the 'no motor function' health state.
- The visits to occupational therapy and a physiotherapist assumed by the Company are significantly higher than UK clinical practice.
- The number of hospitalisations in the Company submission is an over-estimate.
- Hospitalisation and A&E visit frequencies in UK practice are similar.
- Patients in the UK are likely to visit an ophthalmologist one to two times a year.
- Some patients in the UK are likely to be referred to an otolaryngologist.
- Patients in the UK are likely to visit pulmonologists twice per year.

The company accept these updates to the base case (Table 6).

Table 6: Revised Company base case: Annual number of follow-up visits, hospitalisations, and A&E attendances for each health state (based on EAG expert advice)

Resource use	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Dietician	2.00	2.00	1.00	1.00	1.00
Endocrinologist	0.00	0.00	0.00	0.00	0.00
Gastroenterologist	2.50	2.50	2.08	1.65	1.65
General practitioner	2.13	2.13	1.79	1.45	1.45
Geneticist	0.00	0.00	0.00	0.00	0.00
Neurologist	2.50	2.50	2.08	1.65	1.65
Nurse	2.50	2.00	1.00	1.00	1.00
Occupational therapy	28.00	28.00	22.23	15.00	15.00
Ophthalmologist	1.50	1.5	0.43	0.10	0.10
Orthopaedic surgeon	0.13	0.13	0.16	0.20	0.20
Otolaryngologist	1.00	1.00	0.50	0.50	0.50
Paediatrician	1.50	1.50	1.55	1.60	1.60
Physiotherapist	60.00	60.00	50.00	30.00	30.00
Pulmonologists	2.00	2.00	1.00	0.00	0.00
Psychiatrist	0.50	0.50	3.33	6.15	6.15
Psychologist	0.00	0.00	0.00	0.00	0.00
Speech therapist	16.31	16.31	26.35	36.40	36.40
Hospitalisation	0.75	0.75	0.60	0.50	0.50
A&E attendance	0.75	0.75	0.60	0.50	0.50

Source: this is an adjusted version of CS Table 58, but with the number of follow-up visits, hospitalisations and A&E attendance adjusted to reflect clinical advice received by the EAG.

Annual medical and technical procedure resource use per motor milestone health state:

Similar to the above, the EAG's clinical expert largely agreed with the Company's assumptions for medical and technical procedures. The EAG's clinical expert recommended the following changes:

- Patients in the no motor function or full head-control health states may need a barium swallow test.
- Patients in the no motor function state are likely to have 1-2 blood tests per annum.
- Folic acid and prolactin are not used in UK practice.
- Patients are unlikely to have "glycaemia NT dosage in CSF" resource use or annual lumbar punctures in UK clinical practice
- Urine vanillactic acid level tests are not routinely performed in the UK (only at diagnosis)
- Hip and spine X-rays are performed 6-monthly in the UK, depending on the child.

The company accept these updates to the base case (Table 7).

Table 7: Revised Company base case: Medical procedure annual resource use by motor milestone health state (based on EAG expert advice)

Medical procedure	No-motor function	Full-head control	Sitting unassisted	Standing with support	Walking with assistance
Barium swallow test	1.00	1.00	0.09	0.00	0.00
Blood test	1.50	0.88	0.87	1.00	1.00
Coagulation test (PT, INR, PTT)	0.75	0.75	0.73	0.90	0.90
Electroencephalography	0.75	0.75	0.75	0.75	0.75
Folinic acid dosage in CSF	0.00	0.00	0.03	0.03	0.03
Glycemia NT dosage in CSF	0.00	0.00	0.00	0.00	0.00
Iron dosage	0.88	0.88	0.87	1.00	1.00
Lumbar puncture	0.00	0.00	0.00	0.00	0.00

MRI (cerebral)	0.35	0.35	0.26	0.15	0.15
ECG	0.75	0.75	0.88	1.30	1.30
Non-Bruininks-Oseretesky test	0.00	0.00	0.00	0.00	0.00
Plasma AADC dosage	0.00	0.00	0.00	0.03	0.03
Prolactin dosage	0.00	0.00	0.00	0.00	0.00
Urine test	0.75	0.75	0.81	1.00	1.00
Urine vanillactic acid level	0.00	0.00	0.00	0.00	0.00
X-ray (hip)	2.00	2.00	2.00	0.00	0.00
X-ray (pelvis)	0.25	0.25	0.13	0.00	0.00
X-ray (spine)	2.00	2.00	2.00	2.00	2.00

Source: this is an adjusted version of CS Table 59, but annual resource use adjusted to reflect clinical advice received by the EAG.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The mean age of the modelling population is lower than expected in clinical practice.	Section 4.2.4	No	The EAG's clinical expert advice was that the mean age of 4 years and mean weight of 11.1kg, as used as the Company's base case, is lower than expected in clinical practice. The EAG therefore, preferred a mean age of 6 years and mean weight of 15kg as the base case. Other than this, the EAG provide no reference for their preferred model assumption of a mean age of 6 years and a mean weight of 15kg. The Company believes a mean age of 4 years and mean weight of 11.1kg is more appropriate and representative of the eligible population than the EAG preferred assumption as it is derived directly from the eladocagene exuparvovec trials (see section B.2.3.1.1 and section B.3.2.1 of the CS) and aligns directly with the clinical effectiveness data employed in the model. The Company also notes that the EAG's clinical expert could not comment on whether the trial population baseline weight was representative of the UK population baseline weight (page 41 of EAG report), and the EAG's clinical expert also said the trial population was *"generally representative of the people with AADC deficiency seen in clinical practice*." (page 42 of EAG report). While we acknowledge that patients may be diagnosed later in the UK than in Taiwan, the pathway of care incorporating eladocagene exuparvovec in the clinical setting will aim to identify, diagnose and treat patients when they are as young as possible as this may allow patients to gain the full effects of the technology. This is supported in the marketing authorization granted by the EMA which states that "the treatment effect tends to be more pronounced in children who are younger".[25] In line with this, the GOSH clinical expert consulted by the Company during technical

			engagement expects that, over the years following eladocagene exuparvovec's approval, the average age of patients at the time of treatment will decrease as GOSH will move more quickly to intervene due to the potential for better outcomes in patients treated at a younger age. Further anecdotal evidence indicates that the age of diagnosis and treatment in SMA has decreased since the approval of onasemnogene abeparvovec. The company would also like to highlight that the study used to derive survival estimates for the economic model (Brooks *et al.* (2014) [24]), for which the EAG deemed a "reasonable" approach and agreed with the use of CP as a proxy disease based on expert advice, had a baseline age of 4 years. This means that survival estimates in the model are also based on a mean age at baseline of 4 years, meaning the model survival estimates align to the trial population.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 8: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 8 in the EAG report: The survival extrapolation methods used by the company overestimate survival	The Company's preferred base-case before technical engagement was the extrapolation of survival estimates using the log-logistic distribution for the no-motor function, full-head control, sitting unassisted, standing with support health states, and the exponential distribution for the walking with assistance health state.	The Company have revised the selection of the base-case survival curves to Weibull for the no-motor function, full-head control, sitting unassisted, standing with support health states.	**ICER:** £[redacted] (PAS price) This is a decrease of £2,719 from the Company's original base-case ICER of £[redacted]. **ICER:** £172,992 (list price) This is a decrease of £3,625 from the Company's original base-case ICER of £176,617.
Issue 9 in the EAG report: It is unclear how reflective the company's resource use estimates are of clinical practice	Please see Issue 9 for a detailed breakdown of the Company's base case before and after the technical engagement based on the following four criteria:	• See Table 4 for the Company's revised pre- and post-operative resource use and costs associated with the administration of eladocagene exuparvovec in response to the technical engagement.	**ICER:** £[redacted] (PAS price) This is an increase of £4,121 from the Company's original base-case ICER of £[redacted].

	• Pre- and post-operative costs associated with eladocagene exuparvovec administration. • The proportion of patients treated with each treatment category in the best supportive care basket per motor milestone state. • Annual number of follow-up visits, hospitalisation, and A&E attendance inputs for each health state. • Annual medical and technical procedure resource use per motor milestone health state.	• See Table 5 for the Company's revised proportion of patients treated with each BSC treatment category in response to the technical engagement. • See Table 6 for the Company's revised resource use inputs for the annual number of follow-up visits, hospitalisation, and A&E attendance in response to the technical engagement. • See Table 7 for the Company's revised resource use inputs for the annual medical and technical procedures in response to the technical engagement.	**ICER:** £180,738 (list price) This is an increase of £4,121 from the Company's original base-case ICER of £176,617.
	• The Company's base-case number of caregivers before technical engagement for each motor milestone was 2.2, 1.95, 1.7, 1.45, and 1.2, for no motor function, full-head control, sitting unassisted, standing with support and walking with assistance, respectively. • The Company used 2019/2020 prices in their base-case before technical engagement. • The Company modelled TEAE's affecting ≥20% of	• The Company have revised the number of caregivers for each motor milestone as to align with the suggested numbers given by the EAG in the EAG report; 2.5 caregivers for the no motor function health state and 2 caregivers for the remaining health states. • The Company updated the costs given in the economic model to 2021/2022 as suggested by the EAG in the EAG report. • The Company include TEAE's affecting >5% of patients in the revised base-case as suggested by the EAG in the EAG report.	**ICER:** £[redacted] (PAS price) This is an increase of £471 from the Company's original base-case ICER of £[redacted]. **ICER:** £177,149 (list price) This is an increase of £532 from the Company's original base-case ICER of £176,617.

	patients in their base-case before technical engagement.	• In addition to the above, the Company accepts the EAG corrections to the economic model as stated on page 128/129 of the EAG report.	
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: £[redacted] (PAS price) Incremental costs: £[redacted] (list price)	£[redacted] (PAS price) £176,227 (list price)

Sensitivity analyses around revised base case

The Company has rerun the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) around the revised base-case described in **Error! Reference source not found.**. The results using the PAS price are presented below.

Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was conducted using the revised base-case, in which applicable parameters were varied by either using the upper and lower bounds of 95% confidence intervals or +/- 20% if confidence intervals are unavailable.

Using the list price, Figure 1 and Figure 2 present the impact on incremental QALYs and incremental costs from the OWSA for eladocagene exuparvovec versus BSC. Figure 3 presents the impact on the ICER from the OWSA for eladocagene exuparvovec.

Using the PAS discount price, Figure 4 and Figure 5 present the impact on incremental QALYs and incremental costs from the OWSA for eladocagene exuparvovec versus BSC. Figure 6 presents the impact on the ICER from the OWSA for eladocagene exuparvovec.

Table 9 and Table 10 show the results for the top 10 most sensitive parameters from the OWSA.

The main drivers of the incremental QALYs are caregiver disutility for patients with no-motor function, sitting unassisted, standing with support and full-head control. The main drivers of the incremental costs are the resource use for occupational therapy and a physiotherapist for patients in the no motor function health state, as well as for patients in the sitting unassisted health state.

The main drivers of the ICER are caregiver disutility for patients with no-motor function, sitting unassisted, standing with support and full-head control.

Figure 1: OWSA: Eladocagene exuparvovec vs BSC: Incremental QALYs (list price)

Abbreviations: BSC – best supportive care; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use; Util - utilities

Figure 2: OWSA: Eladocagene exuparvovec vs BSC: Incremental costs (list price)

Abbreviations: BSC – best supportive care; FHA – full head control; NMF – no motor function; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use

Figure 3: OWSA: Eladocagene exuparvovec vs. BSC: ICER (list price)

Abbreviations: BSC – best supportive care; FHA – full head control; NMF – no motor function; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use; Util - utilities

Table 9: OWSA most sensitive parameters for ICER impact (list price)

Parameter	Lower	Upper	Difference
Caregiver disutility: No-motor function			
Caregiver disutility: Sitting unassisted			
Caregiver disutility: Standing with support			
Caregiver disutility: Full-head control			
Util: No-motor function			
Util: Sitting unassisted			
Util: Standing with support			
Util: Walking with assistance			
Util: Full-head control			
NMF BSC: RU Occupational therapy			

Abbreviations: BSC – best supportive care; FHA – full head control; ICER – incremental cost-effectiveness ratio; NMF – no motor function; OWSA – one-way sensitivity analysis; QALY – quality-adjusted life year; RU – resource use; Util – utilities

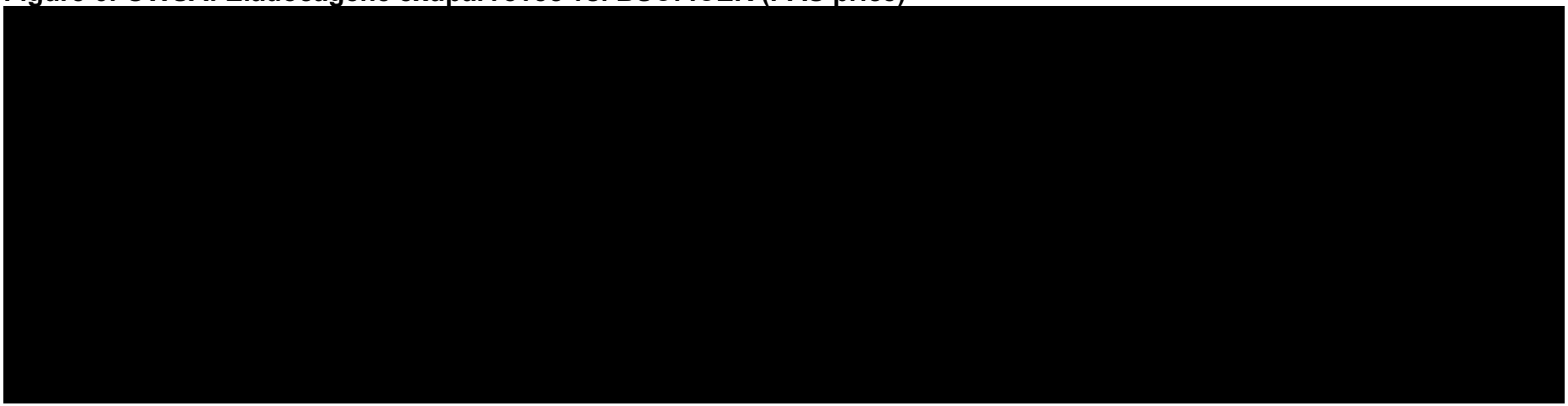
Figure 4: OWSA: Eladocagene exuparvovec vs. BSC: Incremental QALYs (PAS price)

Abbreviations: BSC – best supportive care; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use; Util - utilities

Figure 5: OWSA: Eladocagene exuparvovec vs. BSC: Incremental costs (PAS price)

Abbreviations: BSC – best supportive care; FHA – full head control; NMF – no motor function; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use

Figure 6: OWSA: Eladocagene exuparvovec vs. BSC: ICER (PAS price)



Abbreviations: BSC – best supportive care; FHA – full head control; NMF – no motor function; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use; Util - utilities

Table 10: OWSA most sensitive parameters for ICER impact (PAS price)

Parameter	Lower	Upper	Difference
Caregiver disutility: No-motor function			
Caregiver disutility: Sitting unassisted			
Caregiver disutility: Standing with support			
Caregiver disutility: Full-head control			
Util: No-motor function			
Util: Sitting unassisted			
Util: Standing with support			
Util: Walking with assistance			
NMF BSC: RU Occupational therapy			
Util: Full-head control			

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; NMF – no motor function; OWSA – one-way sensitivity analysis; PAS – patient access scheme; QALY – quality-adjusted life year; RU – resource use; Util – utilities

Probabilistic sensitivity analysis

A PSA was explored in the CEA to explore uncertainty in the revised base-case results. The PSA jointly samples from the assigned distribution of each model parameter included 1,000 times.

Table 11 summarizes the results from the PSA using the list price of eladocagene exuparvovec. In the PSA using the list price, the ICER is £[redacted] per QALY gained for eladocagene exuparvovec versus BSC. The incremental per patient costs with eladocagene exuparvovec versus BSC are £[redacted] and the incremental per patient QALYs gained are [redacted]. The results of each probabilistic model run are presented on the cost-effectiveness plane for eladocagene exuparvovec and BSC (Figure 7 and Figure 8). Figure 9 and Figure 10 present the cost-effectiveness acceptability curves (CEAC) and the cost-effectiveness acceptability frontier (CEAF) using the list price.

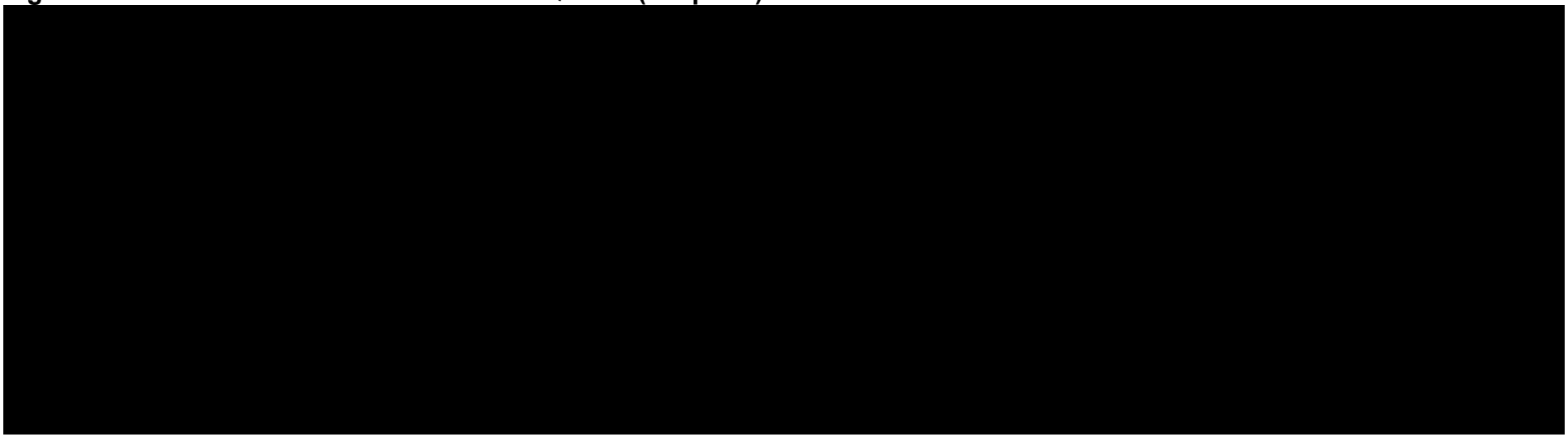
Table 12 summarizes the results from the PSA using the PAS discount price of eladocagene exuparvovec. In the PSA using the PAS price, the ICER is £[redacted] per QALY gained for eladocagene exuparvovec versus BSC. The incremental per patient costs with eladocagene exuparvovec versus BSC are £[redacted] and the incremental per patient QALYs gained are [redacted]. The results of each probabilistic model run are presented on the cost-effectiveness plane for eladocagene exuparvovec and BSC (Figure 11 and Figure 12). Figure 13 and Figure 14 present the CEAC and the CEAF using the PAS price.

Table 11: Total costs, QALYs and ICER from the PSA (list price)

	Total costs (95% CI)	Total QALYs (95% CI)	ICER (95% CI)
BSC	[redacted]	[redacted]	[redacted]
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]

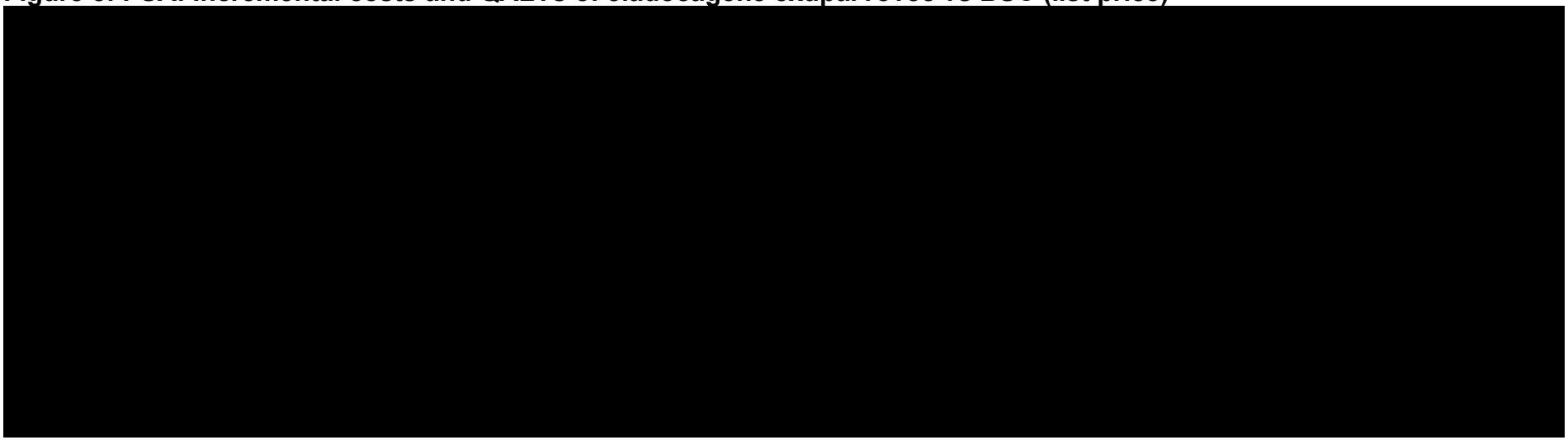
Abbreviations: BSC – best supportive care; CI – confidence interval; ICER – incremental cost effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

Figure 7: PSA: Total discounted costs and QALYs (list price)



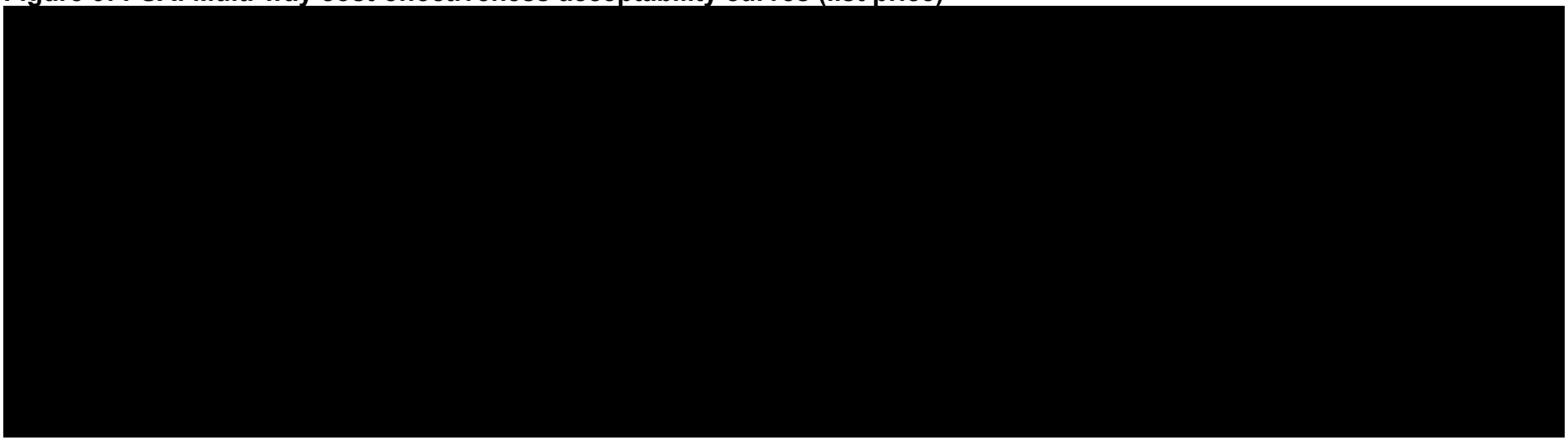
Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 8: PSA: Incremental costs and QALYs of eladocagene exuparvovec vs BSC (list price)



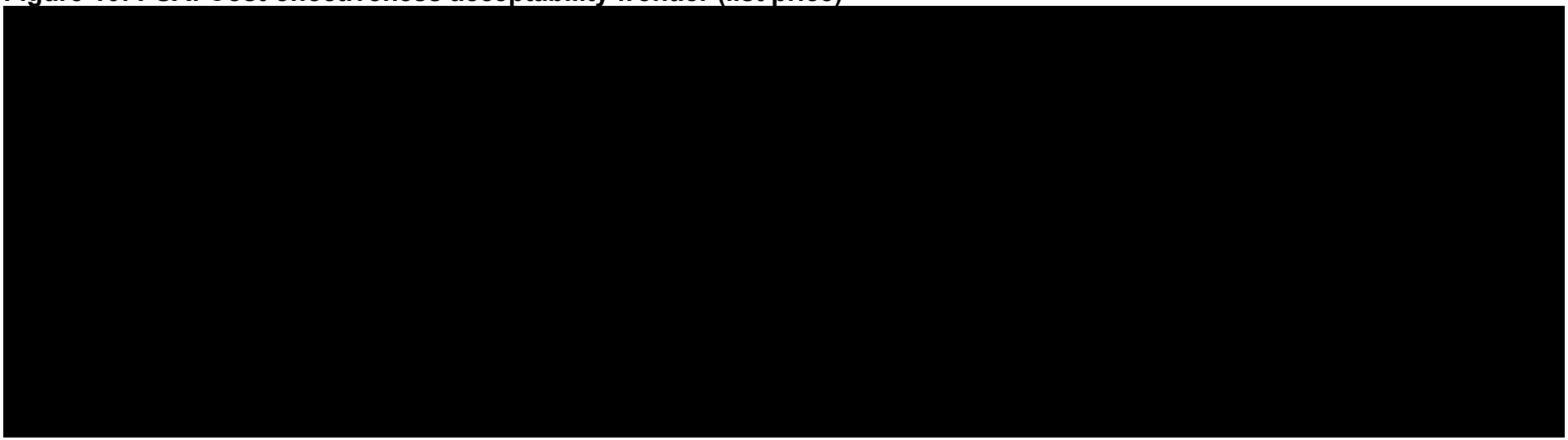
Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 9: PSA: Multi-way cost-effectiveness acceptability curves (list price)



Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 10: PSA: Cost-effectiveness acceptability frontier (list price)



Abbreviations: BSC - best supportive care; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Table 12: Total costs, QALYs and ICER from the PSA (PAS price)

	Total costs (95% CI)	Total QALYs (95% CI)	ICER (95% CI)
BSC	[redacted]	[redacted]	[redacted]
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – best supportive care; CI – confidence interval; ICER – incremental cost effectiveness ratio; PAS – patient access scheme; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

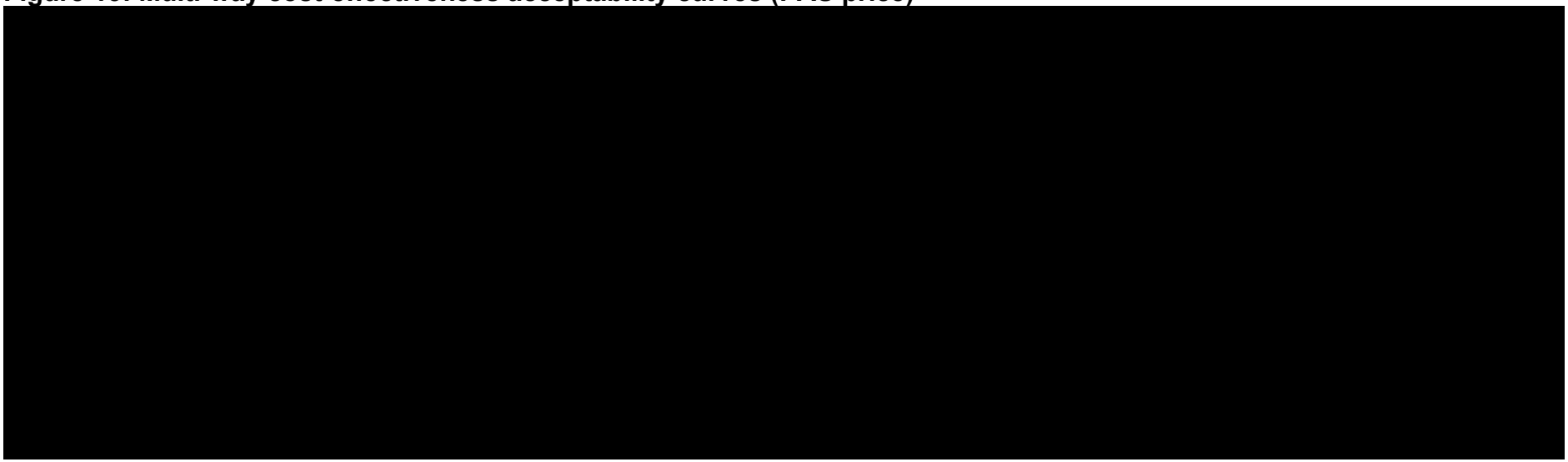
Figure 11: PSA: Total discounted costs and QALYs (PAS price)

Abbreviations: BSC - best supportive care; PAS – patient access scheme; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 12: PSA: Incremental costs and QALYs of eladocagene exuparvovec vs BSC (PAS price)

Abbreviations: BSC - best supportive care; PAS – patient access scheme; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 13: Multi-way cost-effectiveness acceptability curves (PAS price)



Abbreviations: BSC - best supportive care; PAS – patient access scheme; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Figure 14: PSA: Cost-effectiveness acceptability frontier (PAS price)

Abbreviations: BSC - best supportive care; PAS – patient access scheme; PSA - probabilistic sensitivity analysis; QALY - quality-adjusted life year

Scenario analysis

A number of scenarios were explored using the revised base-case to investigate the impact of using different assumptions, values and data sources for model inputs based on the CS and the EAG report. The results of the scenario analysis are presented in Table 13 using the PAS price. The scenario analysis shows that the CEA using the revised base-case is most sensitive to the QALY modifier, the 3.5% discount rate on costs and QALYs and the utility values from HST 15.

Table 13: Scenario analysis results for the Company's revised base-case (PAS price)

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
Base case	-	[redacted]	[redacted]	[redacted]
QALY modifier applied	QALY modifier not applied	[redacted]	[redacted]	[redacted]
Population: 4 years, 11.1kg	Population: 2 years, 8.5kg	[redacted]	[redacted]	[redacted]
	Population: 6 years, 15kg	[redacted]	[redacted]	[redacted]
Discount rate - QALYs: 1.5%, costs: 1.5%	QALYs: 3.5%, costs: 3.5%	[redacted]	[redacted]	[redacted]
	QALYs: 0%, costs: 0%	[redacted]	[redacted]	[redacted]
Model specification: Gompertz (28 patients)	Model specification: Asymptotic (28 patients)	[redacted]	[redacted]	[redacted]
Length of developmental phase: 12 years	Length of developmental phase: 9 years	[redacted]	[redacted]	[redacted]
Modelling motor milestones through Bayesian growth model	Modelling motor milestones though observed distribution (LOCF approach)	[redacted]	[redacted]	[redacted]
	Modelling motor milestones though observed distribution (distribution per follow-up)	[redacted]	[redacted]	[redacted]
Development based on NHDB	NHDB-based development: No improvement for patients on BSC	[redacted]	[redacted]	[redacted]
	NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]	[redacted]	[redacted]
Expected survival (Brooks 2014): CP. Weibull for all health states except walking with assistance [exponential])	Expected survival (Brooks 2014): CP. Weibull for all health states	[redacted]	[redacted]	[redacted]
	Expected survival (Brooks 2014): CP. Log-logistic for all health states except walking with assistance [exponential])	[redacted]	[redacted]	[redacted]

Base case setting	Scenario explored	Incremental costs	Incremental QALYs	ICER
	Best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	[redacted]	[redacted]	[redacted]
	Expected survival (Oskoui 2007, Zerres 1997): SMA	[redacted]	[redacted]	[redacted]
Adverse events: occurring in >5% of patients	Adverse events: occurring in ≥20% of patients	[redacted]	[redacted]	[redacted]
Source of utility: TTO study (UK)	Health state utilities from HST 15	[redacted]	[redacted]	[redacted]
	Health state utilities from Buesch *et al.*			
	Source of utility: SG study (UK)			
	Source of utility: DCE study (UK), scenario 1	[redacted]	[redacted]	[redacted]
	Source of utility: DCE study (UK), scenario 2	[redacted]	[redacted]	[redacted]
Caregiver disutility source: Acaster (2013)	Carer disutility: 'QoL study on AADC deficiency'	[redacted]	[redacted]	[redacted]
2 caregivers for all health states except no motor function (2.5 caregivers)	Numbers of caregivers per health state: No-motor function 2.20, Full-head control 1.95, Sitting unassisted 1.70, Standing with support 1.45, Walking with assistance 1.20	[redacted]	[redacted]	[redacted]

Abbreviations: *CP – cerebral palsy; kg – kilogram; NHDB – natural history database; QALY – quality-adjusted life-year; TTO – time-trade off*

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating aromatic L-amino acid decarboxylase deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Simon Heales
2. Name of organisation	AADC Research Trust and Neurometabolic Unit, National Hospital, Queen Square, London
3. Job title or position	Medical and Scientific Director of AADC Research Trust. Director of the Diagnostic Laboratory
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with aromatic L-amino acid decarboxylase deficiency? ☒ A specialist in the clinical evidence base for aromatic L-amino acid decarboxylase deficiency or technology? ☒ Other (please specify): Clinical Biochemist with 30 years plus experience in the laboratory diagnosis and monitoring patients with AADC deficiency – CSF profiling. Supervise PhD students on disease mechabisms.
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for aromatic L-amino acid decarboxylase deficiency? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Dopamine agonists, MAOIs, Pyridoxine/Pyridoxal phosphate, folinic acid, melatonin.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in aromatic L-amino acid decarboxylase deficiency?	From a biochemical point of view – yes there is an unmet need. For AADC, it is currently very difficult to successfully address the underlying biochemical deficiencies.
11. How is aromatic L-amino acid decarboxylase deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	From a biochemical perspective, there is evidence that there is correction of the dopamine pathway. This biochemical correction is likely to be responsible for meaningful clinical outcomes.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	From a biochemical point of view, the trial addresses the primary underlying enzyme deficiency.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Uncertainty whether all relevant data have been included in the CS	
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	
It is unclear how the observed trial data on motor milestone achievement used in	

the model for eladocagene exuparvovec was derived	
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	
Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	
Use of PDMS-2 scores to predict motor milestone achievement	
Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	
The survival extrapolation methods used by the company	

overestimate survival	
It is unclear how reflective the company's resource use estimates are of clinical practice	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This is the first treatment to address the primary cause of AADCd, i.e correction of the enzyme deficiency.
- The dopamine pathway appears to be adequately addressed and this is reflected by a corresponding increase in the CSF metabolite, homovanillic acid.
- There appears to be little effect on the serotonin pathway, as judged by evaluation of the CSF metabolite, 5-hydroxyindoleacetic acid; patients will therefore still have a deficiency of this neurotransmitter and this will need to be acknowledged.
- Patients with AADCd are at risk of developing secondary folate deficiency, as a consequence of an increased generation of 3- methyl dopa. Currently, it is very unclear whether this will remain a problem. Monitoring, of CSF 5-methyltetrhydrofolate status and supplementation with folinic acid may still be required.
- Despite concerns around serotonin, the effects upon dopamine are likely to be responsible for the positive and significant clinical effects.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with aromatic L-amino acid decarboxylase deficiency or caring for a patient with aromatic L-amino acid decarboxylase deficiency. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

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Part 1: Living with this condition or caring for a patient with aromatic L-amino acid decarboxylase deficiency

Table 1 About you, aromatic L-amino acid decarboxylase deficiency, current treatments and equality

1. Your name	Richard Earl Poulin III
2. Are you (please tick all that apply)	☐ A patient with aromatic L-amino acid decarboxylase deficiency? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with aromatic L-amino acid decarboxylase deficiency? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Metabolic Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with aromatic L-amino acid decarboxylase deficiency? **If you are a carer (for someone with aromatic L-amino acid decarboxylase deficiency) please share your experience of caring for them**	The first three months of life seem to happen as would with typical children, but in hindsight, there were small indicators that did not seem serious at the time. Oculogyric Crises (OGCs) began to appear by about three months old. This telltale sign of AADC deficiency was misdiagnosed as epilepsy since it looks similar to spells and seizures. Even if families are fortunate to receive a correct diagnosis, no approved treatments or medications are available that significantly improve minimizing debilitating symptoms of OGCs, dystonia, and autonomic dysfunction. Our daughter went through various medications hoping to alleviate symptoms, but not much was accomplished. With no medication option, we were left trying to care for a child as best we can while minimizing the pain our child suffers through. We connected with other families, and they resorted to medicating their children to sleep, so they do not feel the pain of OGCs and dystonia. We did not go this pathway, but it was a constant idea we debated over. At least one parent must dedicate themselves to full-time caring for and sustaining their child's life. However, a team helps to eliminate the caregivers' physical and mental challenges. For example, AADC deficient children do not sleep well. With a team effort, my wife and I could alternate nights staying up. Ideally, parents hire outside assistance. We dedicated significant time and energy to caring for our daughter, and we still required the help of a full-time nanny. Someone with nursing

	care would offer the greatest hope for survival, but this is done to sustain life and does not offer much in the way of progress. As patient ages, the more difficult it is to care for them due to their weight and size. Feeding is difficult, requiring special attention as patients do not have the muscles to swallow correctly. This increases the risk of choking or aspiration. Even after feeding, a child cannot remain lying flat due to the possibility of aspirating. We had frequent hospital emergency care admissions related to aspiration or lung infection. Even saliva can result in a hospital admission for aspiration. Special feeding equipment is necessary to help improve digestion. Children have temperature instability, usually sweating profusely. Attention to clothing and bedding can ensure a child does not have skin irritation or rashes. More importantly, due to a child's inability to move voluntarily, they must be moved, massaged, and placed in positions to help avoid bone deformity and bed sores. Our daughter had a dislocated hip despite all our efforts. The world of an AADC deficiency parent is very lonely. We did not leave the house much due to fears that our child could become sick, have difficulties feeding, or trigger an Oculogyric Crises. When we did go out, unfamiliar faces, loud noises, or even temperature changes would trigger an anxiety attack. We had to rely on public transportation to get around, which added to the already long list of difficulties. Our favourite location if we did go out was to walk to the park, where we would be in nature and free from people. We had to work to keep her cool and well hydrated. During one outing, she became pale and disoriented. We had delayed giving her breakfast because we wanted to eat at the park. However, her blood sugar levels were unstable. We were unsure what was wrong with her, and once she was at the hospital, the doctors helped her to recover.

	Many parents cannot feed their children sufficiently, or the process is too difficult to avoid aspiration, so they must have a feeding tube or stomach port. This helps to prevent hospital admission, but even with a feeding tube aspiration is a possibility. The doctor recommended that our daughter have a feeding tube due to the number of emergency visits and her low weight. However, we bought expensive baby formula with high calories and spent more than an hour feeding her to help our daughter gain weight. Information and support are limited. Support groups dedicated to AADC deficiency do what they can to help parents care for their children. However, parents are often busy taking care of their children or going to the hospital, so they cannot dedicate time to researching support information, joining parent workshops, or attending training courses. After our daughter received gene therapy, we were able to maintain a normal schedule and typical lifestyle. We began to reflect on our journey and realized that depression and mental health were issues that we were not aware of at the time. This is due to the mental anguish of helplessly watching your child suffer, sleep deprivation, skipping meals, and being overwhelmed with tasks. We were the fortunate ones that had a happy ending that brought us out of depression. Other families continue to watch their child suffer or must deal with complex feelings of saying goodbye to their child.
7a. What do you think of the current treatments and care available for aromatic L-amino acid decarboxylase deficiency on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I am aware there is currently no approved treatments for use in the NHS. We sought health care traveling to Singapore, Thailand and Taiwan. Medications may help slightly to minimize the effects from the debilitating symptoms. For us, medication just made our daughter sleep, and this was not actually addressing the symptom. All the families we work with try to share options for diet and supplements hoping that we something will show as helping to alleviate symptoms.

	Going to the hospital for test or routine check-ups are difficult. Anxiety is high as soon as we arrive at the hospital. Often, we would have to sedate our child to complete a test or to receive a vaccine. We want to care for our daughter, but we know that trying to get her help means a physically and emotionally exhausting. Our community's current view is to try and enrol their child into a clinical trial or compassionate use as soon as possible. Space is limited and enrolment requirements will exclude many families. Conversations are catered around how to get access to this treatment. I have supported 10 families to join gene therapy clinical trials. The others in the community can see the benefits from gene therapy which has only increased their desire to offer the same for their child. Every care giver of an AADC deficiency child is faced with the reality that our children must receive gene therapy or face death.
8. If there are disadvantages for patients of current NHS treatments for aromatic L-amino acid decarboxylase deficiency (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Caregivers of AADC deficiency patients desperately want a cure, and they may worry that this technology is not a full fledge cure. For the full potential of this surgery to be realized, caregivers must dedicate attention to paramedical therapies before and after gene therapy. Results may vary. Finally, they worry about having access to treatment as early as possible.
9a. If there are advantages of eladocagene exuparvovec over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does eladocagene exuparvovec help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Before our daughter had eladocagene exuparvovec gene therapy, we were just trying to keep her alive. She required constant care and supervision. She was in pain, couldn't sleep, and did not eat well. She was bed ridden and only had involuntary movements, usually from symptoms of dystonia. Three months after receiving eladocagene exuparvovec gene therapy in November 2019, our daughter sat up on her own. Since then, she continues to make progress. For physical accomplishments, she can run, kick a ball, jump, swim, and even ride a horse. She does not have the same balance, coordination, or strength as other children her age, but for the most parts others do not realize she even has challenges. She attends school with the aid of a shadow teacher who mainly supports with transitioning to different areas of the school and help on the playground. She goes

	up and down stairs independently, but a shadow teacher or parent is always present as she is still developing this skill. She can hold eating utensils independently and feed herself. Recently she has been working with using a Montessori inspired chopstick for eating. We have never had an issue with difficulty feeding or swallowing. She has never been admitted for emergency care after gene therapy. Being in school, she has been sick, but recovered just as a typical child would. She has travelled to more than ten countries and her immune system has been able to defend against any illness that are likely during transit. Approximately one year after gene therapy, our daughter underwent hip surgery to correct her dislocated hip. Doctors believed the hip never formed correctly due to being bedridden and dystonia may have dislocated the hip early on leading to additional reasons why her pelvic bone never formed properly. She was in a spica cast from her chest to her ankle with a wooden dowel between her legs to keep them stabilized. While in the cast, she would use her arms to pull herself across her play mat. She wanted to move and did not let the cast stop her. After the spica cast was removed three months later, it took some time for her to feel comfortable again. However, eventually she was moving more freely. Our daughter lives in a multilingual house. She speaks English in small phrases and has great comprehension. She can advocate for herself, asks and answers questions, and sing songs. She learned additional phrases in Thai and Chinese and understand the contexts when to use these languages. Most importantly, our daughter was given a chance to live an independent life with meaning and purpose because of eladocagene exuparvovec. Our lives as parents were freed to make memories and enjoy the blessings of parenthood. Saying we can live a relatively normal life is a miracle.

10. If there are disadvantages of eladocagene exuparvovec over current treatments on the NHS please describe these. For example, are there any risks with eladocagene exuparvovec? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Caregivers of AADC deficiency patients desperately want a cure, and they may worry that this technology is not a full fledge cure. For the full potential of this surgery to be realized, caregivers must dedicate attention to paramedical therapies before and after gene therapy. Results may vary. Finally, they worry about having access to treatment as early as possible.
11. Are there any groups of patients who might benefit more from eladocagene exuparvovec or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I believe all patients with AADC deficiency regardless of their phenotype would benefit from gene therapy since they still have a dopamine deficiency. Gene therapy replaces the entire gene meaning patients would produce a higher amount after gene therapy. Severe patients require gene therapy to survive. The younger the patient receives gene therapy the better results. This limits the amount of missed milestones before they have voluntary control over the body. Parents of older children may not see the same benefits or potential.
12. Are there any potential equality issues that should be taken into account when considering aromatic L-amino acid decarboxylase deficiency and eladocagene exuparvovec? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	AADC deficiency patients come from all backgrounds. A higher incidence rate is found in East Asian populations. Families from a lower socio-economical background may not be able to afford hiring outside help or giving up a job to care for their child. Without treatment, there are fewer options for lower income families. My wife and I were able to work as a team. Single parents will be tasked with an unbearable burden and will require assistance. A support network is required, and families that have the capability of providing this can help sustain life until the child is able to receive gene therapy.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Pharmaceutical companies must encourage health care professionals to council carers on the importance of providing paramedical therapies before and after gene therapy to receive the greatest results. Results will always vary, but each patient can maximize their potential with early intervention and a systematic therapy schedule. Offering this drug gives hope to families and encourages all pharmaceutical companies to invest in growing and advancing gene therapy for all diseases. This future improvements in delivery of the vector through robotic assisted surgery making it possible to operate on patients younger or during gestation offering the greatest hope for a full cure.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Uncertainty whether all relevant data have been included in the CS	
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	This is a novel procedure that continues to show the benefits of gene therapy. It should be noted that data is still being collected and showing positive results. The rare disease community all suffer from the difficulties of balancing the need to collect data with the limitations of the population. In addition, while we collect data and wait for approval, other families must wait and suffer the consequences of AADC deficiency.
It is unclear how the observed trial data on motor milestone achievement used in	For our daughter, we visited the physiotherapy center within the same hospital as her surgery and other doctors. The doctor used the Peabody Developmental Motor Scales (PDMS) to assess our daughter. When talking with other parents on how to track their child's progress, we all used the (PDMS).

Patient expert statement

the model for eladocagene exuparvovec was derived	
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	Our daughter is included in this missing data. In January 2020 we were not able to continue to contribute data on the success of our child due to hospitals protocols. Some parents could continue with the clinical trial schedule. We have registered to continue to add to the long-term evaluation study and will provide updated data for our daughter's progress. This will include biomarkers and motor milestones. We look forward to sharing this data and officially providing results two years post-gene therapy.
Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	
Use of PDMS-2 scores to predict motor milestone achievement	Peabody Developmental Motor Scale is a standard assessment I use when viewing student reports at international schools. The benefit of using this assessment is that it is designed to assess the motor skills of children ages birth to 5 years old. The assessment includes gross motor, fine motor, and total motor skills. These can be compared to normative values to determine the developmental gap. Children enrolled in the clinical trial are in this age group. If they are beyond this age group, they will begin at the same beginning milestones as a new born since they have not had much voluntary movements. In the case of our daughter, she stopped meeting her milestones at three months old. After gene-therapy, we began setting goals based on what would be expected as a new born despite her being two years old.

Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	The data provided continues to show 10 years post-gene therapy children make progress. During this time, other children's lives were cut short since they were not able to receive treatment. Before and after gene therapy, the Peabody Developmental Motor Scale was used by our external clinic not affiliated with the hospital. This helped to share data and continue to track progress as a parent.
The survival extrapolation methods used by the company overestimate survival	
It is unclear how reflective the company's resource use estimates are of clinical practice	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Before gene therapy there were frequent emergency visits from secondary issues because of the severe symptoms.
- No treatment or medication to ease the pain or symptoms so we can only watch them suffer and long-term prognosis is bleak if children survive past 7 years.
- Requires 24 hours care resulting in a parent staying home, hiring outside help to sustain life, or both.
- Expensive devices and therapy to help minimize deterioration of life while waiting for gene therapy.
- Life changing effects of gene therapy eladocagene exuparvovec help us live a relatively normal life and enjoy the blessings of parenthood.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating aromatic L-amino acid decarboxylase deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Manju Kurian
2. Name of organisation	GOSH/UCL
3. Job title or position	Professor of Neurogenetics and Honorary Consultant in Paediatric Neurology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with aromatic L-amino acid decarboxylase deficiency? ☒ A specialist in the clinical evidence base for aromatic L-amino acid decarboxylase deficiency or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it MOSTLY ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for aromatic L-amino acid decarboxylase deficiency? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	- To improve the morbidity and mortality risk associated with this condition
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	- Reduction in oculogyric crises - Reduced pain from dystonia/oculogyric crises - Reduced gastrointestinal dysmotility - Reduced need for AADCd medications - Significant advances in motor development – such as achievement of head control, hand function, truncal tone
10. In your view, is there an unmet need for patients and healthcare professionals in aromatic L-amino acid decarboxylase deficiency?	Yes
11. How is aromatic L-amino acid decarboxylase deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	AADC consensus guidelines (Wassenberg et al 2017) Pathway of care is not well defined but seems to follow a pattern – I see most patients in the UK in my specialist NHS clinic and manage their medications and coordinate their surround care It would mean that a child with a diagnosis should be referred to a specialist surgical centre soon after diagnosis for consideration of a gene therapy approach
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Gene therapy is not current standard care for patients with AADCd

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Specialist paediatric centre with expertise in AADCd, neurosurgical expertise, and an expert PICU and neurology wards/ outpatient setting Some training of doctors and nurses and AHP teams/ PICU/ Neurology wards Pharmacy to be trained in handling gene therapy product Surgical set up for stereotactic surgery Some training in after care (PICU/Neurology wards/outpatients)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, this is a potential outcome Yes, this is a potential outcome
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not yet known whether patients of different age groups and different stages in the disease course will respond differently Not yet know whether state of motor development pre-gene therapy affects response Not yet known whether patients with typical vs atypical AADCd will respond differently Not yet known whether pre-gene therapy disease severity will affect outcome
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is a one-off treatment so the families would need to prepare for general anaesthetic and a relatively long neurosurgical operation – so the child would need a detailed anaesthetic evaluation prior to any procedure. After surgery, the care should be relatively straightforward but will involve outpatient visits, LP, developmental assessments etc (these might be a bit more frequent that in patients not having gene therapy

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The child will need to have no contraindications to general anaesthetic or neurosurgery (and a firm diagnosis of AADCd as per the consensus guidelines)
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, gene therapy approach for this condition seems innovative and has the potential to be a 'step-change' in the management of this condition. It meets the unmet need as a potential precision therapy to advance motor development and improve clinical symptoms.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Potential side effects include neurosurgical complications - Haemorrhage - Infection - Scarring and sequelae - Surgical risk - Metabolic decompensation during peri-operative period However, careful management should help reduce the risk of these issues

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In some ways with regard to patient demographic but not in others (the trial population were predominantly Taiwanese/Chinese with a common founder mutation Extrapolation to UK. – the trial patients were broadly similar patient ages to UK population, overlapping clinical features and some UK patients are similarly severe. All patients with AADCd are thought to have disease from loss of gene function. I am not sure surrogate outcome measures would be needed as the outcome measures proposed could be done in the UK I believe there have been some patient deaths in the PTC trials but I am not sure what the causes of these were and whether they were related to the trial? Perhaps there could be clarification in the meeting?
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is a different trial targeting the midbrain (Pearson et al. 2021) and an ongoing trial in the US for a gene therapy study with a slightly different brain target – at some stage it would be useful to compare the results of that trial with the PTC ones.
22. How do data on real-world experience compare with the trial data?	I think there are some similarities (and probably some differences too)
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	None that I am aware of.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Uncertainty whether all relevant data have been included in the CS	
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	More data would be useful
It is unclear how the observed trial data on motor milestone achievement used in	More clarification would be useful

the model for eladocagene exuparvovec was derived	
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	I am not expert in this
Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	I am not expert in this
Use of PDMS-2 scores to predict motor milestone achievement	Seems reasonable in combination with other outcome measures
Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	Yes, I don't think there is enough long term data on this
The survival extrapolation methods used by the company	I am not an expert

overestimate survival	
It is unclear how reflective the company's resource use estimates are of clinical practice	I am not an expert
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

AADCd is associated with significant risk of morbidity and risk of premature mortality
Current medications are rarely disease-modifying and novel precision treatments are needed
AADC gene therapy has the potential to modify disease, improve motor outcomes and reduce symptom burden in AADCd
AADC gene therapy does not appear curative
NHS investment in caring for patients with the gene therapy modified phenotype will be essential

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	The AADC Research Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data, or analyses?	Response
Uncertainty whether all relevant data have been included in the CS	Yes	To the best of our knowledge the three trials in Japan (jRCT2033210641 (1), jRCTs033180309 (2) and UMIN000017802 (3)) were virtually identical to the Taiwanese trials with the exception that their purpose was to examine tolerability, safety and efficacy of AAV-hAADC2 delivered to the putamen, in an older AADCd population. Participants were mostly of Japanese origin with the exception of two patients: one from Russia and one from Australia. The presiding researchers on both the Taiwanese and Japanese trials were Dr Paul Hwu and Professor Shin-ichi Murumatsu, who have worked together on this gene therapy since trials began in 2009. We are also aware of this treatment being made available on a compassionate basis within the EU. Thus far we understand patients in France have received eladocagene exuparvovec on this basis. Data is available containing a brief narrative on efficacy and safety results is available on two AADC patients aged 10 and 11, who were treated with eladocagene exuparvovec. This data was presented at the 7th International Symposium on Paediatric Movement Disorders

		February 2022 (4) and the14th European Paediatric Neurology Society Congress Conference May 2022 by French authors. Through our own search we found, via AMNOG-MONITOR (5), what appears to be an active trial in Germany that began recruiting in August 2022, however we were unable to investigate further as we could not gain access. Data from these more recent compassionate use trials would be valuable as the participants are unlikely to have the founder mutation. The longer-term data for patients enrolled on the older compassionate use trials, collected since 2009, would be valuable to determine length of efficacy. References: (1) jRCT2033210641 Phase I/II Study of Gene Therapy for AADC (2) jRCTs033180309 Gene Therapy for AADC deficiency (3) UMIN000017802 Clinical Research of the Gene Therapy for AADC deficiency (4) 7th International Symposium on Paediatric Movement Disorders February 2022 (5) Eladocagene Exuparvovec - Upstaza® - frühe Nutzenbewertung des G-BA (amnog-monitor.com)
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	No	Efficacy of eladocagene exuparvovec remains a concern for AADCd patients due to the lack of robust long-term data. This treatment is not a cure but a disease modifying therapy. Our concern is that patients may experience a decline in gained motor skills or a complete reversal, over time.

		Additionally, gene therapy, as we understand it, is a 'one-time' only treatment which increases the risks posed by a potential waning of efficacy. The impact of which could be significant and may mean exclusion from future novel treatments. The lack of longer-term data creates uncertainty with regards to outcomes. The lack of clarity on whether or not those without follow up data differed from those who were included, leaves result open to a degree of bias. It is therefore essential that (post operative) a comprehensive follow up programme is established to monitor gene expression and motor skill development (please see comments in EAR Issue 1,7 and Additional Issue 5 and).
It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived	Yes/No	
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	No	The low participation rate due to the rarity of the disease, the many extenuating circumstances that could contribute to the lack of robust data (such as missed appointments due to illness) and, as evidenced in the trial data, the overall majority of participants show either maintenance or improvement of motor development, we find that the use of LCOF for estimating missing data in the pooled analysis to be an acceptable approach. However, it relies on the assumption that participants maintain motor achievement up to 5 years post-surgery and therefore do not experience a decline. Yet a decline is possible, as recorded in the two patients referred to in Tai C-H et. Al (1), at three- and five-years post-surgery, albeit described as due to non-gene therapy related events. There is a lack of clarity from the CS on key information such as whether any other participants (with data) showed a decline over time and how much missing data

		using the LCOF approach were imputed which could significantly alter the outcomes. Moving forward we would like to see a robust programme for the follow up of patients established to capture critical data and avoid further reliance on the LCOF approach (please see Additional Issue 5). References: (1) Tai C-H, Lee N-C, Chien Y-H, et al. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Molecular Therapy 2022;30(2):509- 18
Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	No	Eladocagene exuparvovec is not a cure, it is a disease modifying treatment and therefore, does not restore patients to full or near full health. Whilst there is evidence of improved motor skills and the frequency of some disease associated symptoms, such as oculogyric crises, much of the underlying disease mechanisms remain compromised, in particular serotonin, indoleamine and catecholamine metabolism including melatonin deficiency, norepinephrine/epinephrine deficiency. (Please see Additional Issue 4 & 5)
Use of PDMS-2 scores to predict motor milestone achievement	No	PDMS-2 scores are a valuable tool to predict motor milestone skills, however they are not entirely accurate when evaluating AADCd patients. AADCd is a multi-faceted disease. PDMS-2 as a scale only captures improvements in physical abilities. It does not address the other significant symptoms in AADCd, such as oculogyric crises. Motor milestones are not usually assessed by formal motor scales within NHS clinical practice. Assessment is qualitative and based on clinician judgement through direct observation. The definitions of primary outcomes, including full head control, sitting unassisted, standing with support, and walking with assistance are important, are all valid and

		we agree that it is reasonable to consider both *newly emerging skills and mastery of key motor milestones*, despite the primary endpoint originally being achieving *mastery*. However, it is indicative of our belief that PDMS-2 is not a reliable tool for assessment in AADC patients, that the company's prediction of motor milestone achievement through PDMS-2 scores overestimates the effectiveness of eladocagene exuparvovec when compared with estimates from observed data. In particular, we note that for the 'best' motor milestone state 'walking with assistance' the predicted estimates are significantly higher than the observed distribution. Thus, potentially risking a bias favouring this treatment over best supportive care.
Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	No	AADCd is not described as a degenerative disease and patients can achieve marginal developmental improvements and maintain them without such intervention over their lifetime. However, the lack of any significant long-term (post 10 years) data makes it difficult to quantify the persistence of treatment benefit over a lifetime. Whilst data from the trials suggests that patients generally maintained motor milestone achievement at their longest follow up timepoint, we believe it would be premature to assume that the effects of this treatment will indeed persist over a lifetime and therefore a robust follow up programme must be established to monitor efficacy in patients (please see comments in EAR Issue 2 and Additional Issue 5).
The survival extrapolation methods used by the company overestimate survival	Yes/No	

It is unclear how reflective the company's resource use estimates are of clinical practice	No	The company has underestimated the resource use, particularly with regards to the surgical procedure, including both pre- and post-op care. In our experience, clinical practice for patients receiving this invasive surgery will involve a minimum 7–10 day stay in hospital, including the procedure, followed by a stay in intensive care and then in a paediatric ward to be monitored. Several procedures both pre and post operative will be required, including approximately: • 3 MRI scans • 1 MRA scan • 2 FDOPA PET scans • 2 CSF lumbar puncture. Patients will require follow-up visits by several multi-disciplinary clinicians. Medication and physiotherapies will continue to be an essential requirement post gene therapy. Current NHS clinical practice includes: 1) Medication approximations: • All patients will be prescribed Dopamine agonists, MAO inhibitors, Vitamin B6, Folinic acid and Vitamin D • Half of patients will receive Benzodiazepines, Melatonin • A third will receive dietary supplements • A quarter Anticholinergic agents 2) Annual number of follow-up visits ranging between 1-2 times per year:

		• Dietician • Gastroenterologist • General practitioner • Neurologist • Nurse • Ophthalmologist • Orthopaedic surgeon • Otolaryngologist • Paediatrician • Pulmonologists 3) Therapy sessions ranging between 1–60 per year: • Occupational therapy • Physiotherapist • Psychiatrist • Speech therapist 4) Hospitalisation and A&E admissions ranging between 1–2 per year: • Hospitalisation • A&E attendance 5) Medical procedures ranging between 1-2 times per year: • Barium swallow test • Blood test • Coagulation test (PT, INR, PTT) • Electroencephalography • Folinic acid dosage in CSF • Iron dosage • MRI (cerebral) • ECG • Plasma AADC dosage

		• Urine test • X-ray (hip) • X-ray (pelvis) X-ray (spine) Care providers: • 2 carers unpaid/paid • Social services

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: UK patient population genotype v. the founder mutation	3.2.1.7 Patients' baseline characteristics	Yes	Participants in this trial have the founder mutation; (IVS6+4A>T (c.714+4A >T), considered to be a severe phenotype and associated with severe genotype, prevalent in the Asian population. As such, the presenting data is based on patients having one or both of this specific mutation. This single gene defect was previously shown to have eighty-four mutations with considerable allelic diversity, however a recent publication (Bertoldi et. al 2022 (3)) has identified 420 variants (more than 135 patients so far identified but the numbers should be higher due to misdiagnosis (Himmelreich et al., 2019 (2)) and that these mutations are currently under extensive research to discover how they affect the phenotypic outcome from patient to patient (further details below), therefore general conclusions of efficacy cannot be raised due to the clustered type of patients treated. It is our opinion that the clinical trial results for eladocagene exuparvovec cannot easily be generalised to the UK patient population. The data available does not cover enough mutation variables to quantify the outcome. The UK patient population can currently be divided into two groups; those who have already received gene therapy in Poland to the mid-brain and the remaining few who may be potential candidates for eladocagene exuparvovec.

			There is a significant difference between the patient population in the trial data and the patient population in the UK. Race is linked to genotype and as previously noted, the trial participants are all of Asian origin with the founder mutation. None of the UK patient population share this mutation, but variations of it with a broad range of genotypes found mainly in the White, European, and Pakistani population. We therefore categorically disagree with the statement made in the CS B.2.3.1.1 that "most patients with AADC deficiency in the UK have the founder mutation." The UK patient population will have all presented as a severe phenotype at some point, either autonomically or physically. Phenotypically, a third of this population could be classified as mild to moderate, based on response to medication. The remainder will be classified as mild to severe with a varying medication response. The consensus guidelines (Wassenberg et al., 2017 (1)) states that clear genotype/phenotype correlations have not yet been established … *"There are no clear genotype/ biochemical or clinical phenotype correlations in AADCD except for the homozygous IVS6 + 4A > T splice variant that is associated with a severe phenotype in all cases reported to date, and rare L-Dopa binding site*

			variants that are associated with L-Dopa responsiveness." However, as previously mentioned this is currently under extensive investigation and the full results are soon to be published. The latest review (Bertoldi et. al 2022 (3)) [redacted] *"The clinical trials of gene therapy based on adeno-associated virus delivered either to the putamen [5–10] or to the midbrain [11,12] could have boosted the interest in this rare disease. Gene therapy represents a hope for many patients and is an undoubtful great step for the approach to this disease that has been neglected and misdiagnosed for a long time [13]. Indeed, recent data obtained via whole-genome and whole-exome sequence analyses together with biological samples screening [13] suggest that AADC deficiency is less ultra-rare than suspected.*

			However, gene therapy has been applied taking into consideration the severity of the phenotype, irrespective of the genotype. This could lead to difficulties in interpreting the follow-up data, since the fully functioning AADC enzyme produced by the exogenous inoculation of its cDNA could be present concomitantly (or not) to endogenous AADC variant chains synthesized starting from the mutated gene. This would give rise to a complex AADC protein population." We strongly recommend that: 1) further trials are necessary on variable genotype mutations to test the efficacy of eladocagene exuparvovec on the general AADCd population and validate the existing data. 2) patients should, in the first instance, be treated with medication (according to the consensus guideline) before assessment, on a case-by-case basis for this surgery. (Please see comments in Additional issue 5) References:

			(1) Wassenberg et al., 2017, Orphanet Journal of Rare Diseases 12, 12 (2) Himmelreich et al., 2019, Mol Gen Metabol 127, 19-22 (3) Int. J. Mol. Sci. 2022, 23(19)

Additional issue 2: The description of AADCd patients as bedridden and many will never achieve any motor milestones	2.2.1.3 Phenotypes and course of the disease	Yes	The description in the CS that AADCd sufferers *"are bedridden all their lives, with complete dependence on their carer … [and] many patients will never achieve any motor milestones at any point throughout their lives"* is somewhat misleading. It is extreme to classify AADCd patients as *bedridden.* Patients are mobile albeit with the assistance of mobility aids such as pushchairs or wheelchairs. Whilst we agree that AADCd sufferers are fully dependent on carers it is important to note that, even with a severe form of the disease, many do make (limited) developmental progress and achieve some motor milestones such as partial head control, rolling and supported sitting. The consensus guidelines (Wassenberg et al. (2017 (1)) states that: *"Based on clinical description, cases were broadly classified as mild (mild delay in developmental milestones, ambulatory without assistance, mild intellectual disability), severe (no or very limited developmental milestones, fully dependent), and moderate (in between)."* As described in the publication 'AADC deficiency from infancy to adulthood: Symptoms and

			developmental outcome in an international cohort of 63 patients' (Pearson et. al 2020 (2)) *"Functional independence for routine activities of daily living including mobility, feeding, bathing, and dressing was analyzed for 38 subjects age 5 years and older. Respondents classified 11% (4/38) as completely independent, 18% (7/38) as partially independent, and 71% (27/38) as completely dependent. Of 29 subjects age 5 to 18 years, 62% (18/29) attended school. Of 8 young adults over age 18 years, 2 participated in work outside the home.* *"This retrospective analysis of disease-related symptoms and developmental outcome in an international cohort of patients, aged 6 months to 36 years, revealed that AADCD is associated with a variety of complex motor and non-motor symptoms throughout the lifespan … It also confirmed that, while the majority of currently diagnosed patients have profound motor developmental impairment, some (20% of patients over age 12 months in this cohort) have milder motor impairment and the ability to walk independently."* References: (1) Wassenberg et al., 2017, Orphanet Journal of Rare Diseases 12, 12 (2) Pearson et. al, 2020, J Inherit Dis 43(5): 1121–1130.

Additional issue 3: Oculogyric Crises as a key clinical outcome	3.2.3.1 Efficacy Outcomes	Yes	We believe oculogyric crises must be regarded as a key clinical outcome. It is one of the most distressing symptoms of this disease with an almost universal incidence with varying periods of duration. Research suggests (Pearson et. al 2020 (1)) that oculogyric crises have considerable impact on patients and indicates a potentially life-threatening significance. *"Our findings confirm that OGCs are a near-universal disease feature, and that they occur in the majority of patients of all ages. In our cohort, they were most prevalent (97%) in children between ages 2 and 12 years. Episodes were reported to peak in duration, frequency and severity before age 6 years in many patients. Indeed, episodes lasting longer than 4 hours were typical for 80% of subjects under age 6 years. Of note, for 2 of the deceased subjects, parents reported an OGC as the apparent proximate cause of death, highlighting that OGCs represent not only a weekly burden of hours of symptom management, but may also have the potential to be life-threatening.* References: (1) Pearson et. al, 2020, J Inherit Dis 43(5): 1121–1130.

Additional issue 4 Serotonin deficiency in AADCd patients	3.2.5.5 Other efficacy outcomes	Yes	Eladocagene exuparvovec is not a cure, it is a disease modifying treatment successfully addressing dopamine deficiency. However, serotonin remains deficient affecting the autonomic nervous system, the endocrine system, and the cardiovascular system. The effects of gene therapy on CSF biomarkers of monoamine neurotransmitter metabolism have been measured in Hwu et al., 2012 (1), Chien et al., 2017 (2), Kojima et al., 2019 (3) and Pearson et al 2021 (4). Irrespective of the site of infusions, available published data report an increase in dopamine turnover, as reflected by the CSF dopamine metabolite homovanillic acid (HVA) but little effect upon serotonin metabolism, as indicated by the CSF 5-hydroxyindoleacetic acid concentration (5-HIAA). Failure to address this serotonergic neurotransmitter system therefore leads to a marked perturbation of the tightly controlled HVA to 5-HIAA ratio to above the normal range (normal 1.0 – 3.7), i.e., to values greater than 10 (Pearson et al 2021). Neglecting serotonin (hence also melatonin metabolism, derived from serotonin) needs to be acknowledged and how to address this moving forward should be considered.

			References: (1) Chien et al., 2017, Lancet Child Adolesc Health 1, 265-273 (2) Hwu et al., 2012, Sci Transl Med 4, 134ra61 (3) Kojima et al., 2019, Brain 142, 322-333 (4) Pearson et al 2021, Nat Commun 12, 4251

Additional issue 5: Post-op care, data collection and monitoring efficacy		Yes	Patients undergoing this invasive procedure report an acute lack of post operative care and support. Patients and their carers experience extreme anxiety as they try to navigate the subsequent stages of this treatment. Post-surgery, patients are discharged with follow ups ranging from 12–18 months. We suggest that a comprehensive follow up programme is established to ensure that patients continue to be both supported and monitored. It is critical that: 1) Longitudinal data is be obtained to safeguard children undergoing this procedure. 2) Therapeutic and clinical involvement for the long term follow up of this treatment, will be the best resource to validate a proven efficacy. 3) Such data will capture any adjustments that may be necessary to this treatment in the future. 4) Residual or novel symptoms may result as the body adjusts, which must be monitored and recorded. 5) Follow up measurements of peripheral and CNS markers must continue to be observed long after this treatment, specifically pertaining to 5-MTHF (5-methyltetrahydrofolate) and any markers

			relating to autonomic dysfunctions and cardiovascular risk. 6) Post treatment shows the absence of decrease or even slight elevations in 3-OMD (Hwu et al., 2012 (1), Chien et al., 2017 (2), Kojima et al., 2019 (3) and Pearson et al., 2021 (4) irrespective of the target site of surgery. This could potentiate homocysteine imbalance and the related folate levels and dopaminergic neurotoxicity (as in Parkinson disease patients) possibly leading to cardiovascular risk (Graham et al., 1997 (5)). This should be acknowledged and considered, as the implication is that patients will continue to remain at risk of developing a central folate deficiency post treatment. 7) Much of the underlying disease mechanisms remain compromised, particularly regarding to indoleamine and catecholamine metabolism including melatonin deficiency, norepinephrine/epinephrine deficiency. 8) In addition, the increased pressure on children to achieve physically from the newly acquired dopamine function may actually cause stress on a system where the level norepinephrine/epinephrine remains unknown. 9) Serotonin – please see additional issue (4) 10) As this treatment is not a cure the follow up data may necessitate altering the criteria for patient eligibility. Such criteria must ensure they are safe for inclusion and the right

			services are included post treatment for example, cardiology. 11) Medications will remain an important adjunct to this treatment and as such it is important to record data on those that can be eliminated, adjusted, or introduced. 12) A comprehensive therapeutic care plan including physiotherapy, must be established in order for patients to fully benefit from newfound motor function. References: (1) Hwu et al., 2012, Sci Transl Med 4, 134ra61 (2) Chien et al., 2017, Lancet Child Adolesc Health 1, 265-273 (3) Kojima et al., 2019, Brain 142, 322-333 (4) Pearson et al 2021, Nat Commun 12, 4251 (5) Graham et al., 1997, JAMA 277, 1775-1781

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty whether all relevant data have been included in the CS	Yes/No	
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	~~Yes~~/No	The lack of longer term efficacy data beyond 5 years is of significant concern as it is not clear what additional clinical support may be required and how this will impact on the need for additional therapeutic, medical and social support
It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived	Yes/No	
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	Yes/No	

Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%		
Use of PDMS-2 scores to predict motor milestone achievement		
Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	~~Yes~~/No	See previous response
The survival extrapolation methods used by the company overestimate survival	Yes/No	
It is unclear how reflective the company's resource use estimates are of clinical practice	~~Yes~~/No	The rarity of the disease and the fact that there is no formally commissioned service (and therefore no specification outlining service requirements) and the range of clinical and therapeutic inputs mean that these estimates are likely to vary significantly from patient to patient.

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Evidence Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency (ID3791)

Evidence Assessment Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Neelam Kalita, Senior Research Fellow, Health Economics Inês Souto Ribeiro, Senior Research Assistant, Health Economics Karen Pickett, Senior Research Fellow, Evidence Synthesis Emma Maund, Research Fellow, Evidence Synthesis
Correspondence to	Dr Karen Pickett Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	27/09/2022

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LIST OF ABBREVIATIONS

AADC(-d)	Aromatic L-amino acid decarboxylase(-deficiency)
A&E	Accident and Emergency
CS	Company submission
EAG	External Assessment Group
HST	Highly Specialised Technology
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
kg(s)	Kilogram(s)
LOCF	Last observation carried forward
MRA	Magnetic resonance angiography
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PDMS-2	Peabody Developmental Motor Scales Second Edition
PET	Positron emission tomography
QALY	Quality-adjusted life year
TE	Technical engagement
UK	United Kingdom

1. Introduction

This document is the Evidence Assessment Group's (EAG) summary and critique of the response by the company, PTC Therapeutics, to the key issues for technical engagement (TE) proposed in the EAG report for this appraisal (submitted to the National Institute for Health and Care Excellence (NICE) on 22nd July 2022). The EAG received the company's response on 14th September 2022.

The company's TE response form contains the following information:

- A written response to each of the nine key issues, three of which include new evidence and/or analyses (see **Error! Not a valid bookmark self-reference.**).
- Written responses to one additional issue raised by the company, which does not include new evidence and/or analyses (see Table 1).
- A revised base case cost-effectiveness analysis, incorporating a majority of the EAG's preferred assumptions and the corrected cost for intensive care unit (ICU) stay (per stay) (as pointed out by the EAG in the NICE technical engagement teleconference on 18th August 2022).

In this report we present the following:

- Our critique of the company's response to each of the nine issues for technical engagement (section 2).
- A critique of the company's response to the additional issue they raised (section 2).
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of an updated EAG base case and scenario analyses (section 3).

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Uncertainty whether all relevant data have been included in the company submission (CS)	No
2	Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	Yes
3	It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived	Yes
4	Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies	Yes
5	Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	No
6	Use of Peabody Developmental Motor Scales Second Edition (PDMS-2) scores to predict motor milestone achievement	No
7	Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	No
8	The survival extrapolation methods used by the company overestimate survival	No
9	It is unclear how reflective the company's resource use estimates are of clinical practice	No
Additional issue 1	The mean age of the modelling population is lower than expected in clinical practice	No

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Uncertainty whether all relevant data have been included in the CS

2.1.1 Summary of the issue

The Evidence Assessment Group (EAG) identified three studies of AAV-hAADC-2 administered into the putamen, which had been conducted in Japan and which were not listed as either included or excluded studies in the original company submission (CS) systematic literature review. The EAG noted that a publication of the results of these studies (Kojima et al., 2019)[1] stated that the AADC-expressing AAV vector used in the studies was similar to that in the company's eladocagene exuparvovec studies. We assumed that this probably meant that it was not the same, but suggested that confirmation that the studies conducted in Japan were not relevant to the appraisal would be useful. We also suggested that clinical experts and other stakeholders were consulted during technical engagement to establish if they were aware of any other relevant evidence that may not have been included in the CS.

2.1.2 Critique of the company's response

In their response to technical engagement, the company confirmed that the vector used in the studies conducted in Japan[1] is not the same one as used for eladocagene exuparvovec. The company stated that the details of this proprietary vector are not available to the company. The company confirmed that the data from these studies are not relevant to the appraisal. The EAG therefore believes that it is acceptable that this evidence was not included in the CS.

In their response to this issue, the company also provided comments on other evidence the EAG had identified in our report as potentially relevant to this appraisal, namely:

- The PTC-AADC-GT-002 study (NCT04903288) – a single arm, ongoing study designed to primarily assess the safety of the SmartFlow® cannula for delivering eladocagene exuparvovec. The company argue in their technical engagement response that the study is not relevant to the appraisal, because data are not yet available (the estimated primary completion date is July 2023) and because the study is of a short duration (the measurement period runs from baseline up to Week 8). As the study is primarily focused on the safety of the cannula and data are not yet available, we believe it is not an issue that this study was not included in the company's CS. However, as noted in our EAG report, and as reported on the clincialtrials.gov record for this study, the study includes an extension phase which

will capture additional outcomes, including changes in motor development and AADC-specific symptoms, and so may provide further relevant evidence on the clinical effectiveness of eladocagene exuparvovec when it is complete.

- Two conference abstracts reporting data on two people with AADC deficiency who were treated with eladocagene exuparvovec published by authors located in France.[2 3] In their technical engagement response, the company stated that at the time of their submission and when their systematic literature review was conducted, the abstracts had not been published. The company note that as little data are reported in the abstracts and that the company do not have access to other data from the patients described, the evidence cannot be used in this appraisal. The EAG agree that this is reasonable. We note brief, narrative findings reported in the abstracts of improvement in motor function, sleep disturbance, irritability, cognitive development and other aspects of the condition. The authors note transient dyskinesia five to six weeks after eladocagene exuparvovec administration and no serious adverse events.[2 3] One participant was followed-up for nine months and the other for six months.[2]
- The AADC-1602 study – a long-term follow-up of participants enrolled in the AADC-010, AADC-011 and AADC-CU/1601 trials beyond the trial periods. The company note that the long-term data from this study were included in the CS. The EAG note that the company provided a narrative summary of the long-term efficacy results at the clarification questions stage of the appraisal in response to a clarification question A21. The data were from a January 2022 data-cut (clarification response A21). It was unclear to the EAG from the CS if the follow-up data beyond the 12-month end of the AADC-011 trial had been included in the company's economic model (see Issue 3). The company confirmed in their response to Issue 3 that [redacted] of the 10 enrolled participants had data at the February 2020 data-cut used for the economic model and were included in the model.

2.2 Issue 2 – Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery

2.2.1 Summary of the issue

The company provided long-term follow-up outcomes for [redacted] of the enrolled 30 participants in the eladocagene exuparvovec studies (in two of the three studies; AADC-010 and AADC-CU/1601) beyond five years post-surgery in their clarification question response A21. However, it was unclear how participants were selected to continue into the long-term follow-up elements of the studies and reasons for attrition. It was therefore uncertain if those who

were followed up differed to those who were not in a way that may potentially bias the results. Therefore, the longer-term impact of eladocagene exuparvovec on motor milestone achievement (and other outcomes) was subject to uncertainty.

2.2.2 Critique of the company's response

In their response to technical engagement the company confirmed that participants from all three studies included in the CS (AADC-010 [N=10], AADC-011 [N=12], and AADC-CU/1601 [N=8]) were invited to provide long term data by enrolling into the longer-term follow-up study AADC-1602.

In summary, the company stated that as of August 2022, the status of AADC-1602 was:

- [redacted] of 30 patients from the three studies included in the CS were enrolled. [redacted] (from study AADC-010 who [redacted]) did not participate in the study as [redacted] and could not attend follow-up visits in Taiwan.
- [redacted] patients from study AADC-010 were enrolled and [redacted] were contributing longer-term follow-up data. The remaining [redacted] did not have long-term follow-up data as they unfortunately died after their Month 12 visit (due to causes unrelated to eladocagene exuparvovec).
- [redacted] patients in study AADC-011 were enrolled. Of these, [redacted] were currently contributing data. [redacted] patients were not yet contributing data, [redacted] due COVID travel restrictions and [redacted] due to only finishing AADC-011 at the end of January 2022. The company expected [redacted] participants to attend AADC-1602 study visits in the future.
- [redacted] patients in study AADC-CU/1601 were enrolled. Of these, [redacted] were providing long term follow up data and [redacted] unfortunately died (due to reasons unrelated to eladocagene exuparvovec treatment) before providing long-term follow up data.

The company highlighted that not all participants had longer-term data at the time of the February 2020 data cut used in the company model.

Given the information provided by the company at technical engagement, the EAG believe that there is no selection or attrition bias in relation to long-term follow up data for eladocagene exuparvovec.

2.3 Issue 3 – It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived

2.3.1 Summary of the issue

From the information provided in the company submission, the EAG were unable to check the accuracy of the pooled proportions of participants from each trial achieving the motor milestones used in a company economic model scenario analysis and the EAG's base case. The EAG requested that the company provide the underlying calculations and rationale used to derive the pooled estimates, reasons for excluding two enrolled participants and a scenario analysis including them, and clarification about whether data collected after 12 months and up to 60 months in study AADC-011 were incorporated into the model.

2.3.2 Critique of the company's response

In their technical engagement response, the company provide further information on: i) the pooled estimates for the motor milestone achievement; ii) reasons for exclusion of the two participants and iii) the inclusion of longer-term data from patients in AADC-011 in the economic model.

A breakdown of the number of patients providing data at different time points is presented in Table 2 of the company's response to Issue 3. At 60 months, motor milestone data was available for [redacted]% (n=[redacted]) of the total participants (N=28).

The company clarified that [redacted] participants from AADC-011 were excluded from the observed distributions in the economic model due to COVID-19 travel restrictions. They argued that inclusion of data from these [redacted] participants would introduce bias in the results against eladocagene exuparvovec as patients required a longer timeframe (>6 months) to demonstrate improvements in motor milestone achievement.

Lastly, they confirmed the longer-term follow-up data from AADC-011 from [redacted] participants who had data beyond the 12-month follow up was included in the economic model.

The additional clarification on the breakdown of the number of participants included in the observed trial data used in the model is helpful but it is still unclear how the model estimates for the last observation carried forward (LOCF) approach were derived as the underlying numerators are not clearly reported (as opposed to the other two approaches). We agree with the company's rationale for excluding the [redacted] participants from AADC-011.

2.4 Issue 4 – Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis of the eladocagene exuparvovec studies

2.4.1 Summary of the issue

Of the eladocagene exuparvovec trials' observed motor milestone achievement results datasets the company included in their CS economic model, the EAG preferred to use the set with missing data imputed using the LOCF approach in our economic model base case. We believed that this approach was appropriate in the context of eladocagene exuparvovec treatment, but noted two uncertainties related to using these data:

1. It was unclear how much missing data were imputed.
2. The LOCF approach relies on the assumption that people maintain their motor milestone achievement over time after being treated with eladocagene exuparvovec. We noted that two participants in the eladocagene exuparvovec studies experienced a decline in their motor scores three- and five-years post-surgery, respectively,[4] but that it was unclear from the company submission if any other participants experienced a decline in motor function over time. It was therefore unclear if it was reasonable to assume that motor function gains would generally be maintained.

The EAG suggested that provision of information about how much data were imputed and whether any other participants experienced a decline at any point between baseline and five years post-treatment would help resolve these uncertainties.

2.4.2 Critique of the company's response

The extent of missing data

In their response to Issue 4, the company sign-post the reader to their response to Issue 3 where they detail the number and proportion of participants included in the economic model (Table 2 in the company's technical engagement response). The information the company provide suggests that a large proportion of missing data were imputed. The number and proportion of the 28 participants included in the eladocagene exuparvovec studies who contributed data to the company's economic model generally declines over time from [redacted]% (n = [redacted]) at 12 months to [redacted]% (n = [redacted]) at 60 months. The EAG suggest that the amount of missing data at each timepoint adds uncertainty to the cost-effectiveness estimates, as treatment outcomes were unknown for a large number of enrolled participants and thus were presumably imputed. We note that the data used in the model comes from a February 2020

data cut. Given that this data cut is from over two years ago, the EAG suggest that it would have been preferable for the company to have used more up-to-date data in the company model (if available), which would have provided more known motor milestone achievement results from participants with further follow-up data. This would have reduced the need for data imputation and resulted in less uncertainty in the results.

Participants experiencing a decline

In their response the company provide further information about the clinical reasons for decline in motor scores in the two participants noted by the EAG and also reiterated that another participant had a fluctuation in the motor milestone attainment in the longer-term follow-up study, which the company originally mentioned in their response to clarification question A21. The company do not comment on whether or not any further participants experienced a decline or fluctuation in their motor scores over time. The EAG does not have access to individual participant data and therefore cannot confirm the general trends over time in participants' motor milestone achievement. If the EAG assumes that no other participants experienced a decline in their motor function, it appears to be appropriate to assume that participants will generally at least maintain their motor milestone achievement over time, when they have missing data, as the LOCF approach assumes. As stated in our EAG report, this is a conservative assumption.

We still conclude that of the observed motor milestone achievement results datasets included in the company's economic model, the LOCF set is our preferred assumption for the EAG base case. The company's technical engagement response, though, suggests that there is uncertainty associated with these results, as a large number of participants did not have data available at the February 2020 cut-off used to inform the model. As we suggest in response to Issue 6, it would be preferable to update the model numbers to reflect more recent clinical effectiveness results, if available, reducing the need to impute data.

2.5 Issue 5 – Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%

2.5.1 Summary of the issue

The EAG considered that it was unclear if eladocagene exuparvovec met the NICE manual[5] criteria for using a discount rate of 1.5%. This is because it is unclear if the treatment will restore patients to full or near full-health and whether the benefits will persist in the long-term (there are currently no data to support persistence of treatment benefit beyond

10 years). The EAG believed that further information and expert opinion on treatment benefit and plausibility of its persistence in the long-term might help resolve this key issue.

2.5.2 Critique of the company's response

In their response to technical engagement Issue 5, the company reiterated their original arguments for using the 1.5% discount rate, as stated in CS Table 39, and provided further clarification in favour of these arguments for applying the 1.5% discount rate. In addition, they cited a previous NICE appraisal - onasemnogene abeparvovec for treating spinal muscular atrophy (Highly Specialised Technology (HST) 15) - where the NICE committee accepted a 1.5% discount rate as they *"acknowledged that onasemnogene abeparvovec has a high one-off cost, whereas the benefits are accrued over the lifetime of the patient"*.[6] Furthermore, the company argued that eladocagene exuparvovec meets the United Kingdom (UK) Treasury Green Book definition for applying a 1.5% discount rate.

The company's further clarification is helpful. Regarding whether or not the benefits are likely to be sustained over a very long period, we accept that one of the strengths of this appraisal is the longer follow-up data of over five years and up to 10 years post-treatment for [redacted]% of the participants ([redacted]/28), although a very small number had data available at exactly 10 years (n= [redacted] participants with data at six years, [redacted] with data at seven years, and [redacted] participants with data at 10 years; company clarification response A21). [redacted] but [redacted] of these [redacted] participants maintained the achievement or emerging attainment of their highest motor milestone achieved. As argued by the company in their technical engagement response, the EAG acknowledges that the mechanism of action of eladocagene exuparvovec means it is theoretically likely people will maintain their motor function improvements over time, but limited trial data are available to support this assumption, with no data available beyond 10 years post-treatment.

We also accept that the 1.5% discount rate was accepted for a similar previous NICE appraisal (HST 15).[6] However, the company's justification for meeting the UK Treasury Green Book criteria is not applicable in this case as the Green Book criteria do not adhere to the NICE recommended discount rate of 3.5%.

The EAG agree with the company's technical engagement response point that it would be useful for "full or near-full health" to be defined in the context of AADC-d. As stated in our EAG report, our expert was not of the opinion that eladocagene exuparvovec was likely to restore patients to full or near-full health. Whether or not eladocagene exuparvovec meets this criterion remains an area of uncertainty that requires further discussion. The long-term

data included in the company's clarification response A21 of what benefits were maintained up to 10 years post-treatment does not detail what the participants' highest motor milestones achieved were that were maintained at their longest follow-up point, making it difficult to discern the exact longer-term outcomes for these participants. In the company's response to technical engagement Issue 5, the company detail [redacted] study participants who could walk freely without assistance [redacted] following eladocagene exuparvovec and [redacted] who could walk, run and talk [redacted] of treatment (reiterating information provided in CS Table 39).

On balance, due to the remaining uncertainties about the persistence of treatment benefit and whether or not eladocagene exuparvovec may return patients to full or near-full health, the EAG presented the results of our base case and scenario analyses for both the 1.5% and 3.5% discount rates. We view that this issue warrants further discussion with clinical experts.

2.6 Issue 6 – Use of Peabody Developmental Motor Scales Second Edition (PDMS-2) scores to predict motor milestone achievement

2.6.1 Summary of the issue

The company chose to use PDMS-2 scores to predict motor milestone achievement results in their CS cost-effectiveness analysis base case. The EAG preferred to use the observed trial data (with the LOCF approach used to impute missing data) and used these in the EAG base case. We suggested that additional clinical expert opinion about the appropriateness of using the PDMS-2 score to predict motor milestone achievement outcomes would help resolve which approach was preferable.

2.6.2 Critique of the company's response

The company reiterated their arguments for using PDMS-2 total scores to predict motor milestones in the cost-effectiveness analysis (as stated previously in the CS Sections B.3.3.1.1.1, B.3.2.2.7 and Appendix J), compared to using the observed trial motor milestone achievements. Their arguments are based on their underlying rationale that using a Bayesian growth model approach based on PDMS-2 scores allows for future motor milestone improvement for up to 12 years (assumed as the duration of development of a healthy child). The LOCF approach, however, assumes that patients maintain their motor milestone achievement but do not improve beyond the time of their last follow-up.

As no new information has been provided here, we view that our concern about using PDMS-2 scores to predict motor milestones remains unresolved.

We acknowledge that the clinical data from the trials show that patients with longer follow-up generally improve in their motor function up to five years post-surgery (as per longer-term follow-up data from study AADC-011 from the January 2022 data cut presented in clarification response A21), but we also note that they generally maintain their highest motor milestone achieved at their longest follow-up timepoint from five years post-surgery up to 10 years (as per the January 2022 data cut presented in clarification response A21). According to the company's response to technical engagement Issue 2 and as per the ad hoc August 2022 analysis, data for [redacted] patients are available now beyond 60 months compared to [redacted] patients in the original data included in the economic model (according to the company's response to technical engagement Issue 2, longer-term data from [redacted] participants in the AADC-CU/1601 study were included in the company cost-effectiveness model). We also note that [redacted] patients from the AADC-011 study now have data at 60 months. Therefore, updating the model numbers to reflect the most recent clinical data seems to be key to better illustrate the motor milestone distribution observed and to provide a more accurate result when using the LOCF approach.

In addition, the EAG notes that shortening the duration of the development phase from 12 years to five years in the company's base case model has a minimum impact on the overall cost-effectiveness results (<£2,000 per quality-adjusted life year (QALY)). This means that the improvements in motor milestone achievement predicted by the company's preferred Bayesian growth model approach that uses PDMS-2 scores between five and 12 years are almost negligible.

2.7 Issue 7 – Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes

2.7.1 Summary of the issue

The company assumed in their base case economic model that the treatment effect of eladocagene exuparvovec persists over patients' lifetimes. We suggested that this assumption was uncertain due to a lack of follow-up data beyond 10 years post-surgery. We suggested that further discussion and clinical expert opinion on whether the treatment effect will likely persist or plausibly wane would be useful to help resolve this uncertainty. The EAG conducted exploratory scenario analyses to explore the impact on the incremental cost-

effectiveness ratio (ICER) if a gradual decline in treatment effect from year 25 onwards was assumed.

2.7.2 Critique of the company's response

The company provide a summary of clinical evidence and underlying biologic mechanism of action of eladocagene exuparvovec to justify their assumption that treatment benefit persists over a patient's lifetime.

Based on our clinical expert's feedback, which concurs with that of the company's expert, we agree that: i) there is no evidence for treatment waning, and ii) people are likely to maintain improvements in their motor function over time due to the continued production of the AADC enzyme. The EAG agree with the company's technical engagement response argument that the eladocagene exuparvovec clinical trials have demonstrated sustained improvement in motor milestones over the follow-up time periods. The company state that all participants treated with eladocagene exuparvovec have had higher PDMS-2 total scores at their longest follow-up timepoint than at baseline. We agree that this is the case based on data provided in Tai et al. (2022).[4] However, we note that data in Figure S2 of this publication shows that three participants had lower PDMS-2 raw scores at their longest follow-up timepoint than they had at interim timepoints between baseline and the longest follow-up visit, although their scores had not returned to baseline levels. Information provided in the company's clarification response A21 suggests that participants generally maintain their highest motor milestone achieved at their longest follow-up timepoint up to 10 years post-surgery. So we believe that, where data are available, there is a general trend for improvements in motor function being maintained up to 10 years after surgery. However, it is uncertain whether these improvements will be maintained over a patient's lifetime due to lack of data beyond 10 years post-surgery. Our exploratory scenarios were conducted to test the impact on the overall cost-effectiveness results, should the treatment effectiveness of eladocagene exuparvovec wane in the long-term. We acknowledge the limitations of these hypothetical scenarios and therefore excluded them from the EAG preferred assumptions in our analyses.

2.8 Issue 8 – The survival extrapolation methods used by the company overestimate survival

2.8.1 Summary of the issue

The EAG noted that using a Weibull distribution to extrapolate survival for "standing with support" and "walking with assistance" health states predicted similar survival beyond 45

years. We were unclear if this was plausible. We also noted that the company's use of the exponential extrapolation method overestimates the survival of people in the "walking with assistance" health state in their base case, which potentially benefits eladocagene exuparvovec. We used an exponential distribution for this state in our base case, but also conducted a scenario analysis using the Weibull distribution for all the health states. We suggested that additional clinical expert opinion about the plausibility of similar survival in the "standing with support" and "walking with assistance" health states may provide more clarity.

2.8.2 Critique of the company's response

The company accepts the EAG's proposed Weibull distribution to extrapolate survival for four health states: no-motor function, full head control, sitting unassisted, and standing with support and consider this issue as resolved. For the remaining health state - 'walking with assistance' - using a Weibull distribution projects similar survival in patients in the 'standing with support' and 'walking with assistance' states beyond 45 years. The company deemed this as implausible based on the feedback they received from two UK clinical experts who argued that an improvement in motor milestone achievement would likely to correspond with an improvement in survival, as well as reduce the risk of secondary complications associated with the condition.

The company also provided clarification regarding their survival estimates for patients in the 'no motor function' health state. For their analysis, the survival estimates are based on cerebral palsy patients who are 'tube-fed only', rather than a weighted average of all feeding types including 'orally fed by others' and 'self-fed' in the "Does not lift head in the prone position" health state in Brooks et al. (2014).[7] The company stated that this assumption aligned with the clinical experts' feedback they received during technical engagement.

The EAG were unable to verify with our clinical expert and hence remain unclear if it is plausible for patients in the 'standing with support' and 'walking with assistance' health states to have similar mortality in the long term beyond 45 years. For completeness, we conducted a scenario analysis using the Weibull distribution for all the health states, which significantly increased the base case ICERs at the 1.5% and 3.5% discount rates (see Table 49 of the EAG report and Table 5 below). It is noteworthy that while we have agreed with the company to use the exponential distribution for extrapolating survival for the 'walking with assistance' health state, we acknowledge that it potentially overestimates survival (as shown in Figure 6 of our EAG report). Therefore, additional expert clinical opinion about the plausibility of similar survival in the 'standing with support' and 'walking with assistance' health states may provide more clarity on this issue.

The company's clarification regarding their calculation for survival estimates for patients in the 'no motor function' health state is helpful. We agree with their argument. However, our conclusion that their predicted approach underestimates survival in the 'no motor function' health state is unchanged as their estimates are lower than those reported for the 'no motor function' health state in cerebral palsy as shown in the study by Brooks et al. (2014).[7]

2.9 Issue 9 – It is unclear how reflective the company's resource use estimates are of clinical practice

2.9.1 Summary of the issue

The clinical expert advising the EAG agreed with most of the resource use estimates used in the company's economic model but identified some discrepancies between the company's estimates and her experience in clinical practice in the National Health Service (NHS). We used our expert's estimates of resource use in our base case but noted that additional expert clinical opinion about resource use would be informative for resolving the resource use assumptions that should be used.

2.9.2 Critique of the company's response

The company accepts the EAG's proposed changes to the following estimates:

- Pre-operative resource use for magnetic resonance angiography (MRA), lumbar puncture, and FDOPA positron emission tomography (PET) scans
- Post-operative resource use for computed tomography (CT), PET, and FDOPA scans
- Proportion of patients treated with best supportive care
- Annual number of follow-up visits, hospitalisation, and Accident and Emergency (A&E) attendance per motor milestone health state
- Annual medical and technical procedure resource use per motor milestone health state.

At the technical engagement teleconference for this appraisal, held on 18th August 2022, we acknowledged that the company's approach to estimating the costs for a paediatric ICU and paediatric ward stay from the National Schedule of Reference Costs as 'per stay' is correct, as applied in their original base case.

In addition to the above discrepancy, we highlighted that the company applied an incorrect cost for ICU stay at £3,305.99 (Cost code: XB01Z, CCU04; Paediatric intensive care unit:

paediatric critical care patients predominate, advanced Critical Care 3) instead of £7,866.03 (Cost code: XB01Z, CCU04; Paediatric intensive care unit: paediatric critical care patients predominate, advanced Critical Care 5). The company accepted this correction and updated their base case analysis and scenario analyses, presented as part of their response to the technical engagement response and discussed below in Section 3.

We have updated the EAG base case model and the EAG scenarios conducted on our base case model by applying: i) the costs of paediatric ICU and paediatric ward stay as 'per stay', and not 'per day'; and ii) the updated cost of paediatric ICU of £7,866.03 inflated to 2021 prices (£8,108.30) (see Section 3). We consider the discrepancies between the company's and the EAG's estimates for resource use as resolved.

2.10 Additional issue 1 – The mean age of the modelling population is lower than expected in clinical practice

2.10.1 Summary of the issue

The company provided further clarification on their rationale for using a mean age of 4 years and mean weight of 11.1 kilograms (kgs) in their base case. They argue that their base case estimates are appropriate as: i) they are derived from the eladocagene exuparvovec trials and therefore are aligned with the effectiveness data employed in the model; ii) an early identification, diagnosis, and treatment of patients is expected in the pathway of care incorporating eladocagene exuparvovec; and iii) consistency with the estimates used in the study by Brook et al. (2014)[7] that was used to derive survival estimates.

2.10.2 Critique of the company's response

We have noted the company's argument. To reiterate our rationale (as stated previously in our response to the factual accuracy check Issue 15), our base case assumption of using a baseline average age of 6 years was based on advice from our clinical expert who stated that the ages of the patients they treat range between 2 and 14 years. As the company have acknowledged, patients may be diagnosed later in the UK than in Taiwan. With respect to the associated average weight, we used the average weight from the lowest quantile (0.4th) for those aged 6 years, which is 15 kgs, based on our expert's advice that people with AADC deficiency tend to be within the lowest centiles for their ages, compared to their peers. The average weight estimate is obtained from the UK-WHO Growth Charts 2009 of boys and girls aged between 4-20 years.

For completeness, we conducted an additional scenario on the revised EAG preferred model below, where we varied the mean age and weight of the population as that of the company's preferred estimates of 4 years and 11.1 kg. This has a very small impact in the model results (see Table 6 below).

3. Updated cost-effectiveness results - EAG summary and critique

3.1 Company's revised base case cost-effectiveness results

The company accepted the following EAG preferred assumptions and applied these to their original base case model following technical engagement. These include:

- **EAG corrections:** as stated in section 5.3.3 of the EAG report.
- **Adverse events:** Occurring in ≥5% of patients in the trials.
- **Extrapolation of survival curves:** Weibull parametric curve to extrapolate survival in all health states of the model, except for the "walking with assistance" (exponential).
- **Update costs to the most recent price:** All costs are updated to 2021/2022 prices.
- **Resource use estimates** based on estimates informed by the EAG's clinical expert for: i) pre-operative resource use for MRA, lumbar puncture, and FDOPA PET scans; ii) post-operative resource use for CT, PET, and FDOPA scans; iii) proportion of patients treated with best supportive care; iv) annual number of follow-up visits, hospitalisation, and A&E attendance per motor milestone health state; and v) annual medical and technical procedure resource use per motor milestone health state.
- **Number of carers:** 2.5 carers for patients in the "no motor function" health state and two carers for the other health states (according to EAG expert's advice).

In addition to the above, following an EAG suggestion proposed at the technical engagement teleconference on 18th August 2022, the company revised the cost for paediatric intensive care unit stay to £7,866.03 (obtained from XB01Z: CCU04; Paediatric intensive care unit: paediatric critical care patients predominate, advanced Critical Care 5).

Lastly, the EAG acknowledged at the technical engagement teleconference that it is appropriate to assume that the costs sourced from the National Schedule of Reference Costs for paediatric intensive care unit stay and ward stay are *per stay* rather than *per day*, in line with the company's original base case.

Table 2 shows the impact of each change on ICER. We checked the implementation of each change in the model and obtained the same results as those reported by the company.

Table 2 Changes applied to the company's original base case following technical engagement (discounted at 1.5%, QALY modifier applied, PAS price for eladocagene exuparvovec)

Preferred assumption	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's original base case (following clarification questions)	[redacted]	[redacted]	[redacted]
EAG corrections (as stated in Section 5.3.3. of the EAG report)	[redacted]	[redacted]	[redacted]
Adverse events: ≥5%	[redacted]	[redacted]	[redacted]
Extrapolation of survival: Weibull for 'no motor function', 'full head control', sitting unassisted' and 'standing with support' + exponential for 'walking with assistance'	[redacted]	[redacted]	[redacted]
Updated costs to 2020/21 prices	[redacted]	[redacted]	[redacted]
Resource use estimates: based on EAG's expert feedback + EAG proposed cost for Paediatric Intensive Care unit stay of £7,866.03 at the technical engagement teleconference [a]	[redacted]	[redacted]	[redacted]
Number of carers: 2.5 for no motor function and 2 for the other health states	[redacted]	[redacted]	[redacted]
Company's base case following technical engagement	[redacted]	[redacted]	[redacted]

[a] NHS reference costs of paediatric intensive care unit stay and ward stay estimated as costs per stay

EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PAS, patient access scheme; QALY, quality adjusted life years.

In addition, we obtained similar results to the company's sensitivity analyses presented in the company's technical engagement response for deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analyses.

3.2 EAG's revised preferred assumptions

Following the technical engagement teleconference, the EAG applied the following changes to our preferred base case model:

- **Cost of paediatric intensive care unit stay and ward stay:** We agree with the company's original assumption and applied the costs sourced from the National Schedule of Reference Costs for paediatric intensive care unit stay and ward stay as costs '*per stay'* and not as '*per day'*.
- **Cost of paediatric intensive care unit stay:** We applied the revised cost of £7,866.03 – obtained from the cost code XB01Z (CCU04; Paediatric intensive care unit: paediatric critical care patients predominate, advanced Critical Care 5) and inflated it to 2021 prices (£8,108.30).

3.3 Cost-effectiveness results based on EAG preferred model assumptions

The cumulative effect of the EAG's preferred model assumptions is shown in Table 3.

Table 3 Changes applied to the EAG preferred base case following technical engagement (discounted at 0%, 1.5% and 3.5%, QALY modifier applied, PAS price for eladocagene exuparvovec)

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER (£/QALY)		
	3.5%	3.5%	3.5%	0%	1.5%
EAG original preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Cost of paediatric intensive care unit and ward stay – per stay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Cost of paediatric intensive care unit stay: £7,866.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case following technical engagement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years.

3.4 Scenario analyses conducted on the EAG's revised preferred assumptions

We re-ran the scenario analyses presented in the EAG report to investigate the impact of the different assumptions in the EAG revised base case. Table 4 and Table 5 present the results of each scenario analysis using the PAS price of eladocagene exuparvovec.

Similar to what we observed prior to the changes made to the EAG's preferred base case following the technical engagement teleconference, the ICER is most sensitive to the QALY modifier, alternative discount rates, short time horizons, the approach used to distribute patients across motor milestone health states (observed data versus Bayesian growth model), the approach used to impute missing data for the observed distribution of patients across motor milestones (based on LOCF, original sample or distribution per follow-up), treatment waning and health state utility values.

Table 6 presents the results of an additional scenario analysis that explores the impact of using the baseline age and weight from the trials (as in the company's base case) in the EAG revised base case (see additional issue 1 above). We note that this assumption has a small impact in the overall results.

Table 4 Company's scenario analyses using the EAG's revised base case (discounted at 0%, 1.5% and 3.5%; QALY modifier applied, PAS price for eladocagene exuparvovec)

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
EAG revised base case following technical engagement	[redacted]	[redacted]	[redacted]
QALY modifier not applied	[redacted]	[redacted]	[redacted]
Bayesian growth model: Asymptotic (28 patients)	[redacted]	[redacted]	[redacted]
NHDB-based development: No improvement for patients on BSC	[redacted]	[redacted]	[redacted]

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]	[redacted]	[redacted]
Survival - best fitting curves which do not cross (in order Log-logistic, Log-logistic, Weibull, Log-logistic, Exponential)	[redacted]	[redacted]	[redacted]
Expected survival (Oskoui 2007, Zerres 1997): SMA	[redacted]	[redacted]	[redacted]
Exclude adverse events disutilities	[redacted]	[redacted]	[redacted]
Exclude adverse events costs	[redacted]	[redacted]	[redacted]
Exclude adverse events disutilities and costs	[redacted]	[redacted]	[redacted]
Source of utility: SG study (UK)	[redacted]	[redacted]	[redacted]
Source of utility: DCE study (UK), scenario 1	[redacted]	[redacted]	[redacted]
Source of utility: DCE study (UK), scenario 2	[redacted]	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]	[redacted]
Source of caregiver disutility: Gani *et al.* (2008)	[redacted]	[redacted]	[redacted]
2.2 caregivers per health state	[redacted]	[redacted]	[redacted]
BSC, best supportive care; EAG, Evidence Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years.			

Table 5 Additional scenario analyses using the EAG's revised base case (discounted at 0%, 1.5% and 3.5%; QALY modifier applied, PAS price for eladocagene exuparvovec)

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
EAG revised base case following technical engagement	[redacted]	[redacted]	[redacted]
Population: 2 years; 8.5kg	[redacted]	[redacted]	[redacted]
Population: 8 years; 17kg	[redacted]	[redacted]	[redacted]
Time horizon: 10 years	[redacted]	[redacted]	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: Bayesian growth model (Gompertz)	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on original sample	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: observed data based on distribution per follow-up	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: lower CrI for the COLM	[redacted]	[redacted]	[redacted]
Motor milestone achievement for EE: upper CrI for the COLM	[redacted]	[redacted]	[redacted]
Motor milestone achievement for BSC: improvement of 3% per year	[redacted]	[redacted]	[redacted]
Motor milestone achievement for BSC: improvement of 5% per year	[redacted]	[redacted]	[redacted]
Treatment waning: gradual from 25 years onwards	[redacted]	[redacted]	[redacted]
Treatment waning: gradual between 25 and 35 years (same health state)	[redacted]	[redacted]	[redacted]
Treatment waning: gradual between 25 and 35 years (BSC distribution)	[redacted]	[redacted]	[redacted]
Treatment waning: sudden decline at 25 years (BSC distribution)	[redacted]	[redacted]	[redacted]
Adverse events: occurring in ≥20% of patients	[redacted]	[redacted]	[redacted]
Survival: Weibull for all health states	[redacted]	[redacted]	[redacted]
Survival: exponential for walking with assistance; log-logistic for the other health states	[redacted]	[redacted]	[redacted]
Health state utilities from Buesch et al.	[redacted]	[redacted]	[redacted]

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
Health state utilities from HST 15	[redacted]	[redacted]	[redacted]
Carer disutility: 'QoL study on AADC deficiency'	[redacted]	[redacted]	[redacted]
AADC, aromatic L-amino acid decarboxylase; BSC, best supportive care; CrI, credible interval; COLM, cumulative ordered logit model; EAG, Evidence Assessment Group; EE, eladocagene exuparvovec; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years; QoL, quality of life.			

Table 6 Scenario analysis changing baseline age and weight on the EAG's revised base case (discounted at 0%, 1.5% and 3.5%; QALY modifier applied, PAS price for eladocagene exuparvovec)

Scenario	ICER (£/QALY)		
	0%	1.5%	3.5%
EAG revised base case following technical engagement	[redacted]	[redacted]	[redacted]
Population: 4 years; 11.1kg	[redacted]	[redacted]	[redacted]
EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life years.			

References

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PTC Therapeutics International Limited
5th Floor
3 Grand Canal Plaza
Grand Canal Street Upper
Dublin 4 D04 EE70
+353 1 9068700
www.ptcbio.ie

Jasdeep Hayre
Associate Director, Technology Appraisals & Highly Specialised Technologies
National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BT
United Kingdom

25th January 2023

Re: NICE appraisal for eladocagene exuparvovec, ID3791

Dear Jasdeep,

Following recent discussions on the ongoing NICE HST (highly specialised technology) appraisal for eladocagene exuparvovec, PTC are pleased to provide an updated offer with a further reduction on the patient access scheme (PAS) to a discount of [redacted] of the list price. This moves the Committee's base case ICER [redacted] the standard threshold of £100,000 per QALY and directly reduces the uncertainty associated with the prediction of clinical effectiveness in the cost-effectiveness model to within an acceptable range. As such, PTC feels it has demonstrated a robust and compelling cost-effectiveness case for eladocagene exuparvovec, enabling a positive recommendation for routine commissioning to be issued.

While there has been discussion on whether a managed access agreement would be relevant to this appraisal given the uncertainties identified by the Committee, [redacted] that brings the NICE's Committee's preferred base case ICER to [redacted] per QALY. The NICE Committee's preferred approach in the cost-effectiveness model was using the predicted Bayesian growth model, which was determined as a "[redacted]. We recognise that the NICE Committee has identified that there is some uncertainty in the accuracy of using the Bayesian growth model to predict the effectiveness of eladocagene exuparvovec in the cost-effectiveness model. The last observation carried forward (LOCF) approach is the only scenario analysis that provides limited insights into the degree of the uncertainty expressed by the Committee and the impact on the ICER. However, it should be noted that the LOCF approach was neither preferred nor accepted by the NICE Committee, [redacted]:

[redacted]

[redacted]

As such, the LOCF scenario provides a clinically implausible estimate of the uncertainty. While the uncertainty related to the ICER regarding this aspect of clinical effectiveness lies somewhere between this value and the NICE Committee's preferred base case (i.e. between [redacted] and [redacted] per QALY), the reality based on the Committee's own view is that the uncertainty does not sit in the middle of a range of equally likely scenarios, but instead is much more probable to be weighted towards the ICER value using the Bayesian growth model approach. The [redacted].

There is also further uncertainty that was recognised by the Committee, namely whether the lower discount rate of 1.5% applies to this appraisal – and when taking this into account, this has a significant impact on reducing the Committee's preferred base case ICER to [redacted]. The uncertainty related to the ICER can be explored further when considering the ICER value using the LOCF method and the lower discount rate of 1.5% ([redacted] per QALY) which [redacted]. In order to facilitate and expedite a timely publication of a positive recommendation, for routine commissioning, [redacted], and rather than continue the legitimate discussion on the eligibility for the 1.5% discount rate, PTC has chosen to accept the Committee's preferred assumption on discount rate, but it should nevertheless be recognised this is another key area of uncertainty.

The offer outlined in this letter, reducing the PAS, is subject to the following:

- NICE issues a positive routine commissioning recommendation for Upstaza based on the revised PAS.
- There is no managed access agreement required as part of this appraisal (i.e. no data collection or commercial agreement with NHS England). [redacted].

[redacted]

We appreciate your continued efforts to work together with us to reach a positive recommendation and provide access, as soon as possible, [redacted].

Kind regards

[redacted] PTC Therapeutics International Limited