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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

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Date completed	22/07/2022 (updated with corrections 10/08/2022)

Source of Funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number NIHR135598.

Acknowledgements

We thank Prof Manju Kurian, Professor of Neurogenetics, Developmental Neurosciences Department, UCL GOS Institute of Child Health, and Consultant Paediatric Neurologist, Great Ormond Street Hospital for providing expert clinical advice to the project team and for reading and commenting on a draft of this report.

We also thank Dr Jonathan Shepherd, Principal Research Fellow, Southampton Health Technology Assessments Centre (SHTAC), for providing a quality assurance review of the draft report.

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.

This report should be referenced as follows:

Kalita, N; Souto Ribeiro, I; Pickett, K; Maund, E; Woods, L; Scott, DA; Hawa, A; Lord, J. Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency*:* A Highly Specialised Technology Appraisal. Southampton Health Technology Assessments Centre, 2022.

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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.

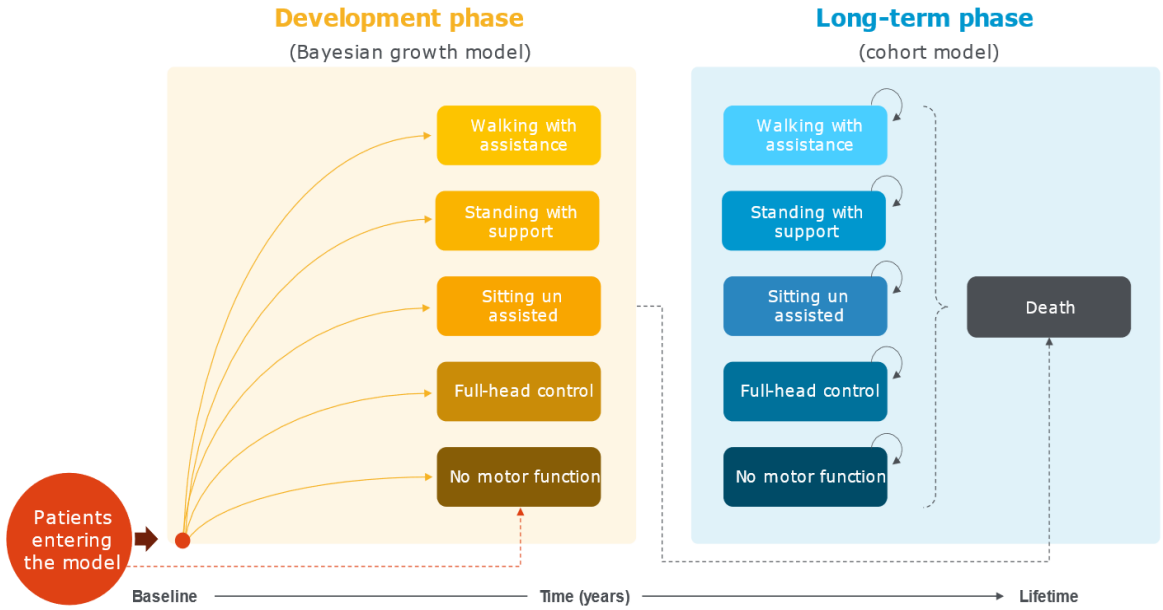


Figure 1 Company's model structure

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

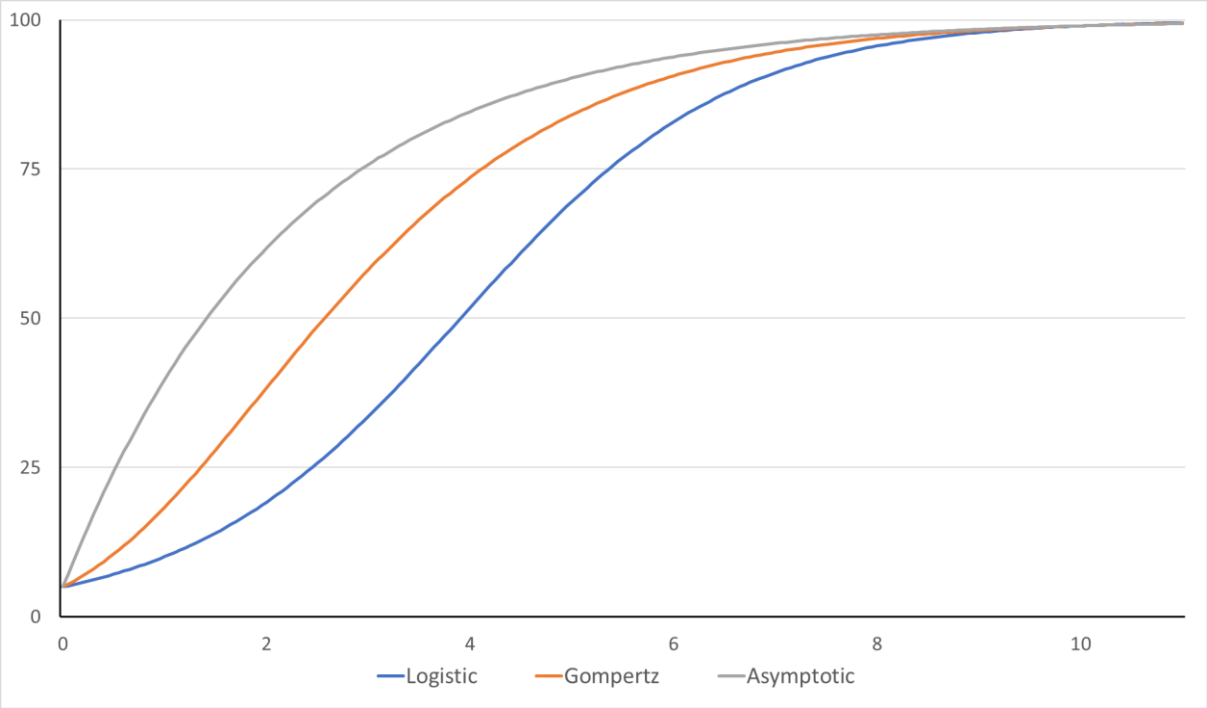
To inform the motor milestone health states, the company used PDMS-2 scores to predict motor milestone achievement; further details on the company's rationale are in CS Section B.3.2.2.7. We present a summary and critique of the company's approach below.

- ***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.

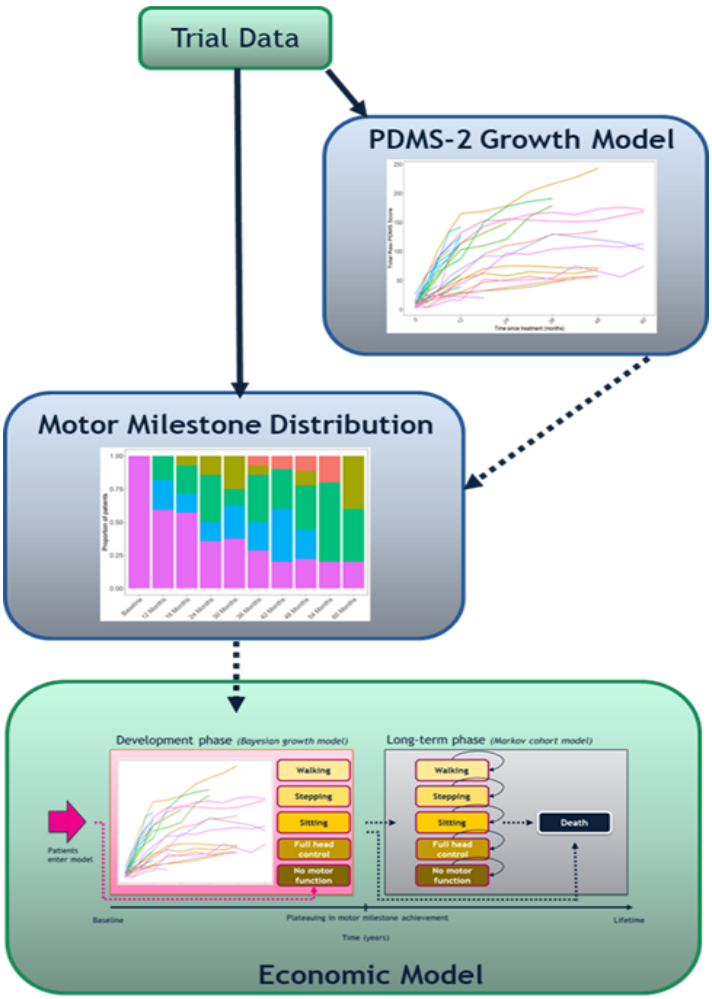


Figure 3 Diagrammatic presentation of the company's approach of using trial data for estimating motor milestone achievement for eladocagene exuparvovec in the model
Source: reproduced from CS Figure 41
Note: Solid arrows indicate estimation of models and dashed arrows represent where estimated fitted 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										

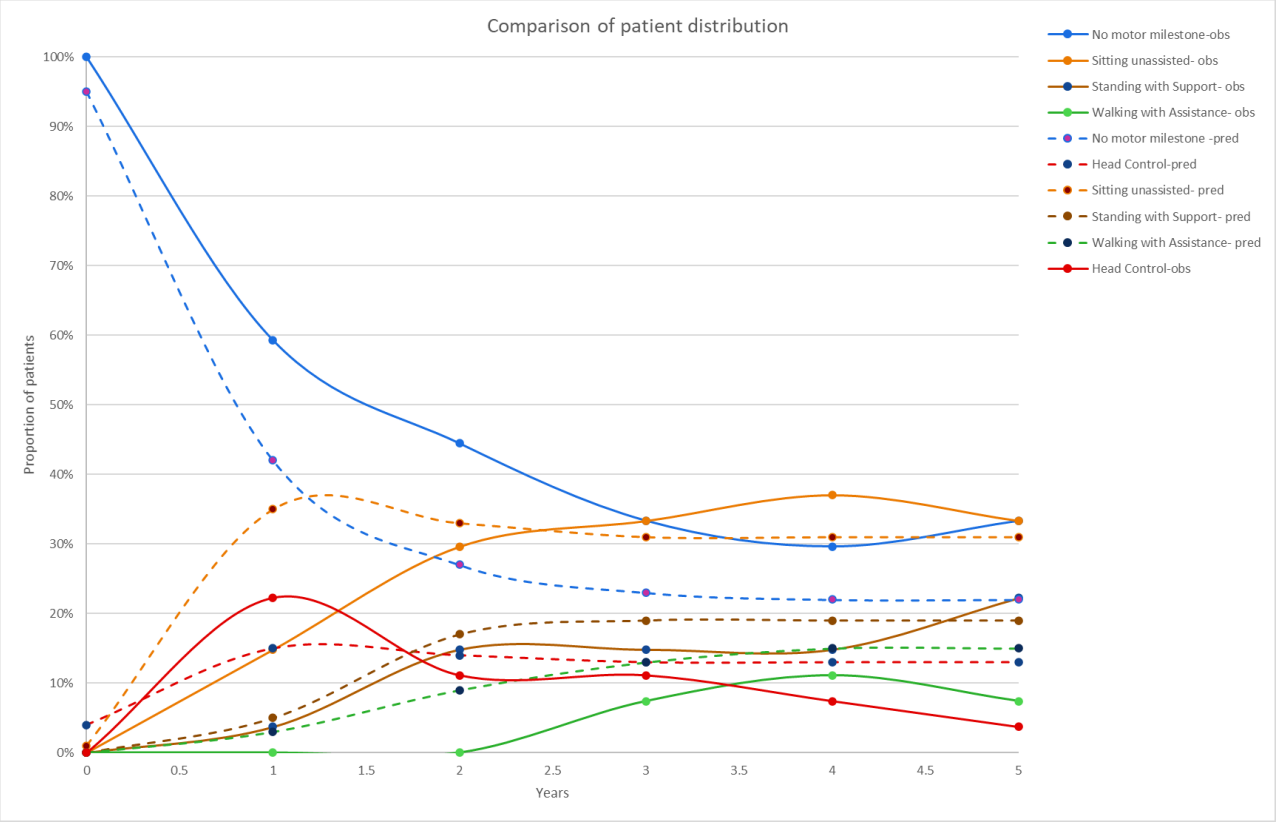


Figure 4 Comparison of patient distribution across motor milestone health states as estimated in the company's base case (using PDMS-2 scores) and scenario analysis (using observed values based on naïve analysis)- eladocagene exuparvovec arm

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.

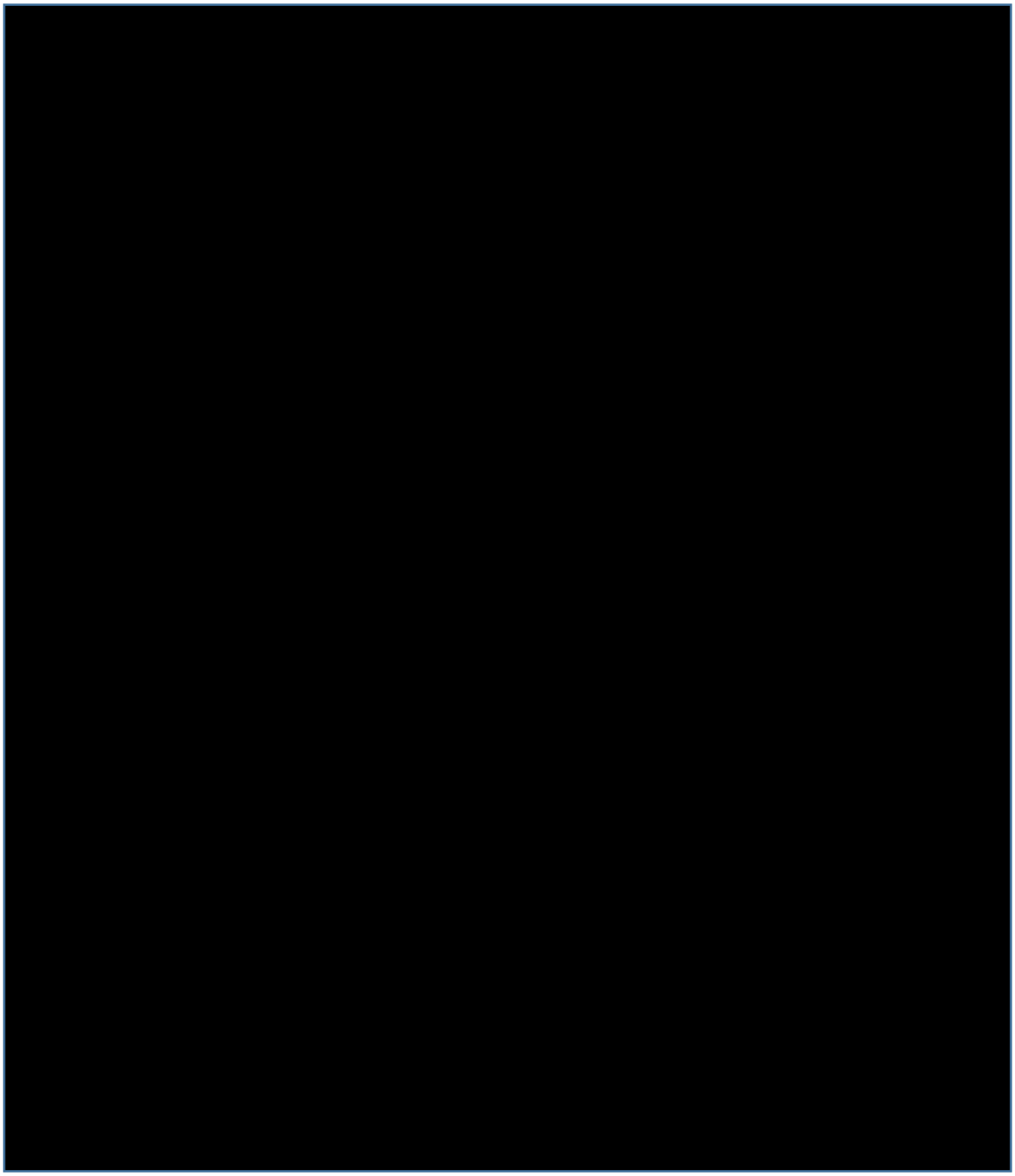


Figure 6 Survival extrapolations for motor milestone health states
Source: reproduced from Figure 5 of the company's response to clarification question B5.
Note: The dotted line represents survival data from Brooks et al.[33]

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).

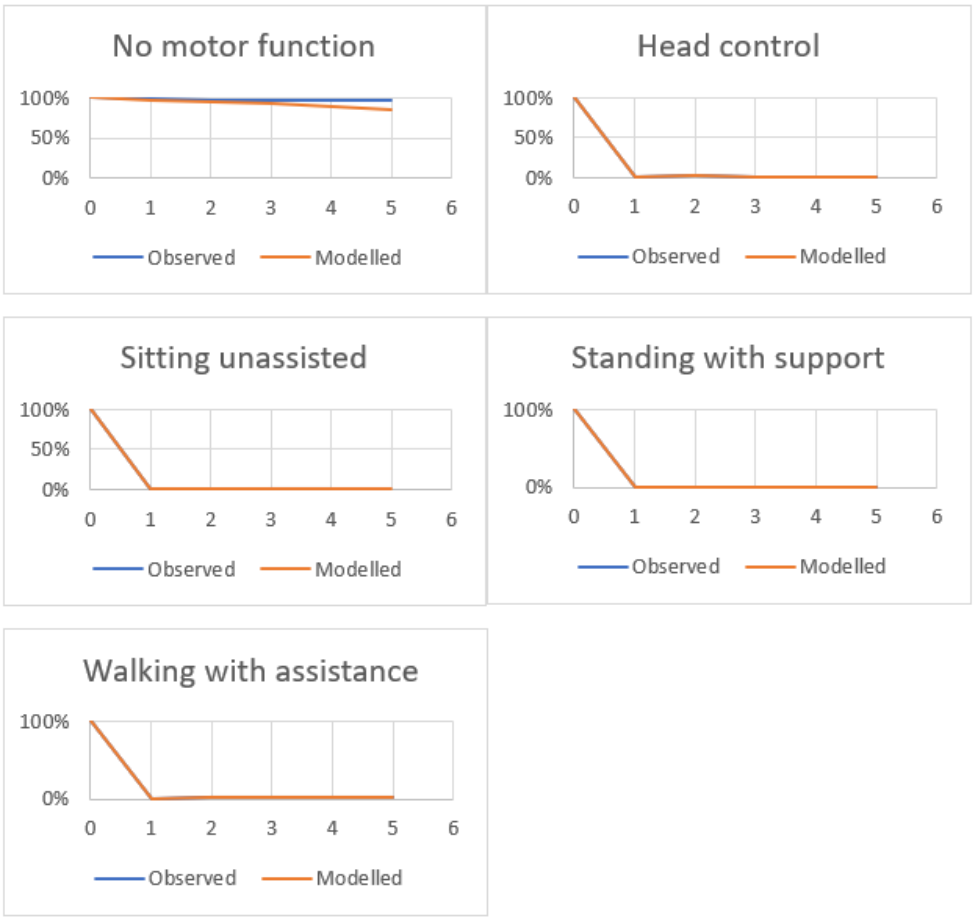


Figure 8 Best supportive care: comparison of motor milestone achievement observed in the NHDB versus modelled estimates
Source: Obtained from CS Table 29; NHDB, natural history database.

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