For public – fully redacted

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

Highly Specialised Technology Committee - 3 November 2022

Chair: Paul Arundel

Lead team: Stuart Davies, Carrie Gardner, Mark Sheehan

Evidence assessment group: Southampton Health Technology Assessments Centre (SHTAC)

Technical team: Luke Cowie, Christian Griffiths, Jasdeep Hayre

Company: PTC Therapeutics

Background on AADC deficiency

A rare genetic disorder with substantial impact on quality and length of life

Causes

- Aromatic L-amino acid decarboxylase (AADC) deficiency is an ultra-rare, genetic disorder that leads to a reduction or absence of AADC enzyme activity, causing reduced levels of serotonin and dopamine.

Symptoms and prognosis

- Most people (80%) with AADC deficiency have severe phenotype, defined as no or very limited developmental milestones and full dependence.
- Most common characteristic of severe AADC deficiency is lack of motor development, with over 95% of patients failing to achieve key motor milestones throughout their shortened lifetime.
- People also suffer a range of neurologic, autonomic, and cognitive impairments (e.g. excessive crying, sleeping problems, irritability, problems with digestion and developmental delay).

Epidemiology

- AADC deficiency occurs at an estimated rate of 1 in 118,000 births in Europe. There are fewer than 12 patients (of any severity) in the UK, equating to a UK prevalence of approximately 1 in 7.5 million people.

Treatment pathway

Current treatment is tailored, symptom-led, multidisciplinary BSC

- No formal clinical treatment pathway or best practice for treating people with AADC deficiency.
- People with AADC deficiency are currently given BSC, wide-ranging symptomatic medications via multidisciplinary team: estimated between 4-14 different medications, and visit a mean of 6 different specialists each year.
- Most commonly used treatments target dopamine pathway, including dopamine receptor agonists and monoamine oxidase (MAO) inhibitors.
- Currently no licensed treatments for AADC deficiency and no treatments that modify disease course.
- After receiving eladocagene exuparvovec, people likely to continue to need multidisciplinary management and a tailored, symptom-led approach to care.

Is BSC the most appropriate comparator?

NICE

AADC, Aromatic L-amino acid decarboxylase; BSC, best supportive care

Patient perspectives (1)

Treatment has potential to address multiple unmet needs

Submissions from The AADC Research Trust & Metabolic Support UK

- Psychosocial and physical impact of living with AADCd is substantial, including for family/caregivers.
- Current treatment options are onerous, burdensome, impact overall quality of life and offer little/no improvement to wellbeing.
- Eladocagene exuparvovec offers multiple advantages including improved quality of life and relieves some, but not all, of the symptoms people experience. Decreases need for 24 hour care, increases independence. Particularly improves muscle control, ability to eat, speech and dyskinesia.
- Some concerns about potential unwanted complications and lack of long term data. Surgical procedure for administering treatment seen as a disadvantage.
- There are multiple unmet needs for people living with this condition. The technology has the potential to improve and address some of these needs.

Patient perspectives (2)

Survey results from The AADC Research Trust and Metabolic Support UK

Living with the condition:

- Most impactful symptoms include: lack of muscle tone (hypotonia), development delays, movement disorders (dyskinesia), excessive sweating (hyperhidrosis), abnormal posture, insomnia, gastrointestinal problems and nasal congestion.
- 75% of respondents said their child uses mobility aids and assistive cognitive aids for daily activities.
- 50% of respondents said they receive care from social services and 37% from a homecare provider.
- 50% of respondents said their child had been admitted to hospital within the last 12 months.

Current treatments:

- Most respondents said prescribed medications provided little improvement to physical health.
- In addition to treatments, most people rely on strict dietary and sleep regimes to manage the condition.
- People also rely on treatments such as physiotherapy and occupational therapy.
- 25% indicated that their child is in receipt of speech and behavioural therapy.

Patient perspectives (3)

4 case studies from The AADC Research Trust and Metabolic Support UK

Case Study 1:

- Since gene therapy, *"every day has been a miracle"*.
- Now able to sit up, run, swim underwater, get out of the pool, currently learning how to jump and was able to recover quickly from a broken bone.
- A *"metamorphosis"* following gene therapy in which a *"paraplegic almost"* child became a *"happy child that's running around".*

Case Study 2:

- Improvements seen after 1-2 weeks following surgery.
- Now able to hold up neck, can open hands from a fist, has eye control and makes new sounds.
- Previously experienced oculogyric crises most days for hours at a time, have not returned since treatment.
- Dystonia now only lasts up to an hour, and is able to sleep alone and much better as a result.
- Although previous medication reduced symptoms, gene therapy is *"solving"* them, and it's been a *"miracle".*

Patient perspectives (4)

4 case studies from The AADC Research Trust and Metabolic Support UK

Case Study 3:

- Since gene therapy has made *"remarkable progress"*.
- Able to deal with infections far better, has stopped tube feeding all together, has reduced medication significantly, can now vocalise and form words, able to sit up independently and now learning how to walk.
- Independence has improved, eating has improved, and last oculogyric crises episode happened 10 days following gene therapy and has not returned since.

Case Study 4:

- Symptoms previously very severe, including oculogyric crises lasting up to 8 hours, every 3 days.
- Since receiving gene therapy has started to control neck and torso, sit up after a few months, make a grabbing motion, has begun to attempt to walk and vocalise.
- After 6 months was able to eat full meals and snacks and experienced *"the joy of food"*.
- Child is *"thriving now"* and *"developing so much more"* than parents expected.
- Perceived disadvantage given was that the gene therapy didn't target the serotonin part of the brain.

Case studies 3 & 4 are from people treated with an alternative experimental gene therapy, not eladocagene exuparvovec.

Patient perspectives (5)

"Eladocagene exuparvovec helped us live a relatively normal life"

Submission from parent & carer of young person treated with eladocagene exuparvovec

- Before gene therapy there were frequent emergency visits because of the severe symptoms.
- Symptomatic treatments often not effective. Parents can only watch them suffer. Long-term prognosis is bleak if children survive past 7 years.
- Requires 24 hours care which is physically and emotionally exhausting. A parent must stay home, hire outside help to sustain life, or both.
- Expensive devices and therapy to help minimize deterioration of life while waiting for gene therapy.
- Life changing effects of gene therapy: helped us live a relatively normal life and enjoy the blessings of parenthood.

"Our daughter went through various medications, but not much was accomplished."

"Before she required constant care and supervision, was in pain, couldn't sleep, did not eat well and only had involuntary movements. 3 months after treatment our daughter sat up on her own, and she continues to make progress. She can run, kick a ball, jump, swim and even ride a horse."

Clinical perspective (1)

Effects upon dopamine responsible for significant clinical benefits.

Submission from AADC Research Trust and Neurometabolic Unit

- This is the first treatment to address the primary cause of AADCd.
- The dopamine pathway appears to be adequately corrected, but there appears to be little effect on the serotonin pathway. People with AADCd will therefore still have a deficiency of this neurotransmitter following treatment with eladocagene exuparvovec.
- People with AADCd are at risk of developing secondary folate deficiency. Currently very unclear whether this is a significant problem. Monitoring and folinic acid supplements may be needed.
- Despite concerns around lack of effect on serotonin pathway, effects on dopamine likely responsible for significant clinical benefits.

Clinical perspective (2)

Submission from clinical expert in paediatric neurology and neurogenetic diseases

- Clear unmet need in AADC deficiency, and treatment has potential to be step change in disease control.
- Expect treatment to improve length and quality of life, but it is not curative.
- Relatively long neurosurgical procedure is not without risk of complications.
- In addition to improved motor milestone achievement, important clinical outcomes include: reduced oculogyric crises, reduced pain, reduced gastrointestinal dysmotility, reduced need for other medications.
- Currently unknown whether treatment outcomes likely to differ depending on age, disease severity or motor milestone development prior to receiving gene therapy.
- NHS investment in caring for patients with the gene therapy modified phenotype will be essential.

Key issues

Issue	Resolved?	ICER impact
It is unclear how the observed trial data on motor milestone achievement used in the model for eladocagene exuparvovec was derived	Partially – for discussion	Unknown
Use of PDMS-2 scores to predict motor milestone achievement	No – for discussion	Large
Appropriateness of using the last observation carried forward (LOCF) approach for estimating missing data in the pooled analysis	No – for discussion	Large
Uncertainty about the longer-term efficacy of eladocagene exuparvovec between >5 years and up to 10 years post-surgery	Partially – for discussion	Unknown
Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes	No – for discussion	Large
Survival extrapolation methods used by the company overestimate survival	Partially – for discussion	Large
Uncertainty whether the current appraisal meets the criteria to apply a discount rate of 1.5%	No – for discussion	Large
Uncertainty whether all relevant data have been included in the CS	Yes	Small
It is unclear how reflective the company's resource use estimates are of clinical practice	Yes	Small

Eladocagene exuparvovec (Upstaza, PTC Therapeutics)

Anticipated marketing authorisation	• Indicated for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype. • EMA marketing authorisation granted 18/7/2022. GB marketing authorisation not yet granted.
Mechanism of action	• Eladocagene exuparvovec is a gene-replacement therapy based on recombinant AAV2 vector containing the human cDNA for the DDC gene. After infusion into the putamen, the product results in the expression of the AADC enzyme and subsequent production of dopamine, and consequently, development of motor function in people treated for AADC deficiency.
Administration	• Eladocagene exuparvovec is a single use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen. A dose of $1.8x10^{11}$ vector genomes (vg) is delivered as four 0.08 mL ($0.45x10^{11}$ vg) infusions (two per putamen).
Price	• List price: £[redacted] • Average cost per patient including administration, treatment acquisition, and monitoring: £[redacted] • A patient access scheme (PAS) involving a simple discount has been approved.

NICE

AADC, Aromatic L-amino acid decarboxylase; AAV2, Adeno-associated virus serotype 2; DDC, dopa decarboxylase; EMA, European Medicines Agency

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Data from 3 open-label, single-arm trials

Study	Population	Intervention, dose	Primary outcome	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 people achieving the following motor milestones: • Full head control • Sitting unassisted • Standing with support • Walking with assistance	5 years+
AADC-CU/1601 Taiwan, n = 8	Children aged ≥2 years with diagnosed AADC deficiency	Eladocagene exuparvovec, $1.8×10^{11}$ vg (n=8)		5 years+
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) • $2.4x10^{11}$ vg* (n = 9)		1 year+

EAG comment: trials generally representative of people seen in UK clinical practice, with exception of race and genotype (all participants in the 3 Taiwanese trials had founder mutation uncommon in Europe. A founder mutation is when a person with a certain mutation becomes one of the initial founders of a new population in an isolated setting, such as Taiwan).

* $2.4x10^{11}$ vg is a higher dose than specified in the marketing authorisation.

PDMS-2
Peabody Developmental Motor Scales Second Edition

Designed to identify developmental delays, this test contains six subtests that assess the motor skills of children:

- **Reflexes (8 items)**
- **Stationary (30 items)**
- **Locomotion (89 items)**
- **Object Manipulation (24 items)**
- **Grasping (26 items)**
- **Visual-Motor Integration (72 items)**

Company view on relevance of PDMS-2 scores:

- Motor milestone achievement was primary outcome in trials for eladocagene exuparvovec, as determined based on the attainment of specific items within the PDMS-2 questionnaire.
- PDMS-2 is a clinically relevant measure of motor development in patients with AADC deficiency, and also used in cerebral palsy (the closest disease proxy to AADC deficiency).

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.

EAG comments:

- Each milestone was measured using one specific item of the PDMS-2.
- EAG expert stated 4 primary outcomes of full head control, sitting unassisted, standing with support and walking with assistance are important and reflect what clinicians look for in clinical practice.
- Reasonable and clinically relevant to consider both 'newly emerging' skills and 'mastery' of milestones.

Clinical trial results: AADC-010 (n=10), AADC-CU/1601 (n=8)

Two trials reported motor milestones (primary endpoint) up to 60 months

Motor Milestone	Timepoint	AADC-010 (n=10) N (%)	AADC-CU/1601 (n=8) N (%)
No motor function	Baseline	10 (100%)	8 (100%)
Head control	Baseline	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]
Sitting unassisted	Baseline	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]
Standing with support	Baseline	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]
Walking with assistance	Baseline	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 60	[redacted]	[redacted]

February 2020 data cut. * n=9, ** n=8 (patients lost to follow up)

Clinical trial results: AADC-011 (n=12)

Trial reported motor milestones (primary endpoint) up to 12 months

- Only 9 of the 12 enrolled subjects were assessed for the primary endpoint: not all subjects were able to return for follow-up visits, primarily due to the COVID-19 pandemic.

AADC-011 - Number and proportion of eladocagene exuparvovec-treated subjects achieving key motor milestones at Month 12

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

- Company did not report data beyond 60 months for studies AADC-CU/1601 and AADC-010 and 12 months for study AADC-011 in original company submission. Some additional data were provided at clarification and technical engagement stages.
- HRQoL was not measured in any of the three studies because patients were “unable to communicate effectively due to being very young and having severe cognitive and language impairment.”
- 9 out of 12 people received a higher dose of eladocagene exuparvovec. Clinical expert advice to EAG is that combining results from both doses is reasonable.

HRQoL, health-related quality of life

Clinical trial results: Oculogyric crisis (secondary outcome)

- **AADC-010:** shows 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]).

- **AADC-011:** (only data up to 3 months reported) shows reduction in oculogyric crisis activity 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.

- **AADC/CU-1601:**

Number of episodes by timepoint

ITC methodology

ITC not feasible, company used natural history database for BSC efficacy

- Company explored the possibility of conducting an ITC to compare the effectiveness of eladocagene exuparvovec to BSC, but ultimately not feasible.
- Instead company compiled a natural history database (NHDB) of people with AADC deficiency. Unique cases (n=49) identified from published reports found through systematic literature review.
- Company did “naïve analysis” of NHDB to estimate proportion of participants who achieved motor milestones over 5 years follow-up while receiving BSC, these proportions used in economic model.

EAG comment:

- EAG considers it uncertain whether all relevant publications have been included in the NHDB.
- Potential risk naïve analysis of BSC in company’s economic model is missing eligible cases.
- Cannot conclude whether NHDB participants were sufficiently comparable to those included in eladocagene exuparvovec studies due to lack of information.
- Agrees with company choice of using naïve analysis of NHDB.

AADC, Aromatic L-amino acid decarboxylase; BSC, best supportive care; ITC, indirect treatment comparison; NHDB, natural history database

Natural History Database-naïve analysis results

Imperfect analysis but most favourable results for BSC

- Naïve analysis, while not adjusting for observed (and unobserved) prognostic factors, is more conservative than each of the adjusted analyses done by company (where fewer BSC participants achieve motor milestones).
- Only 2 BSC participants experienced improvement in motor milestones over five years compared to substantive improvements with eladocagene exuparvovec.

Distribution of patients across motor milestone health states in the BSC arm (derived from the NHDB) and pooled analysis of eladocagene exuparvovec (EE) trials (February 2020 data cut)

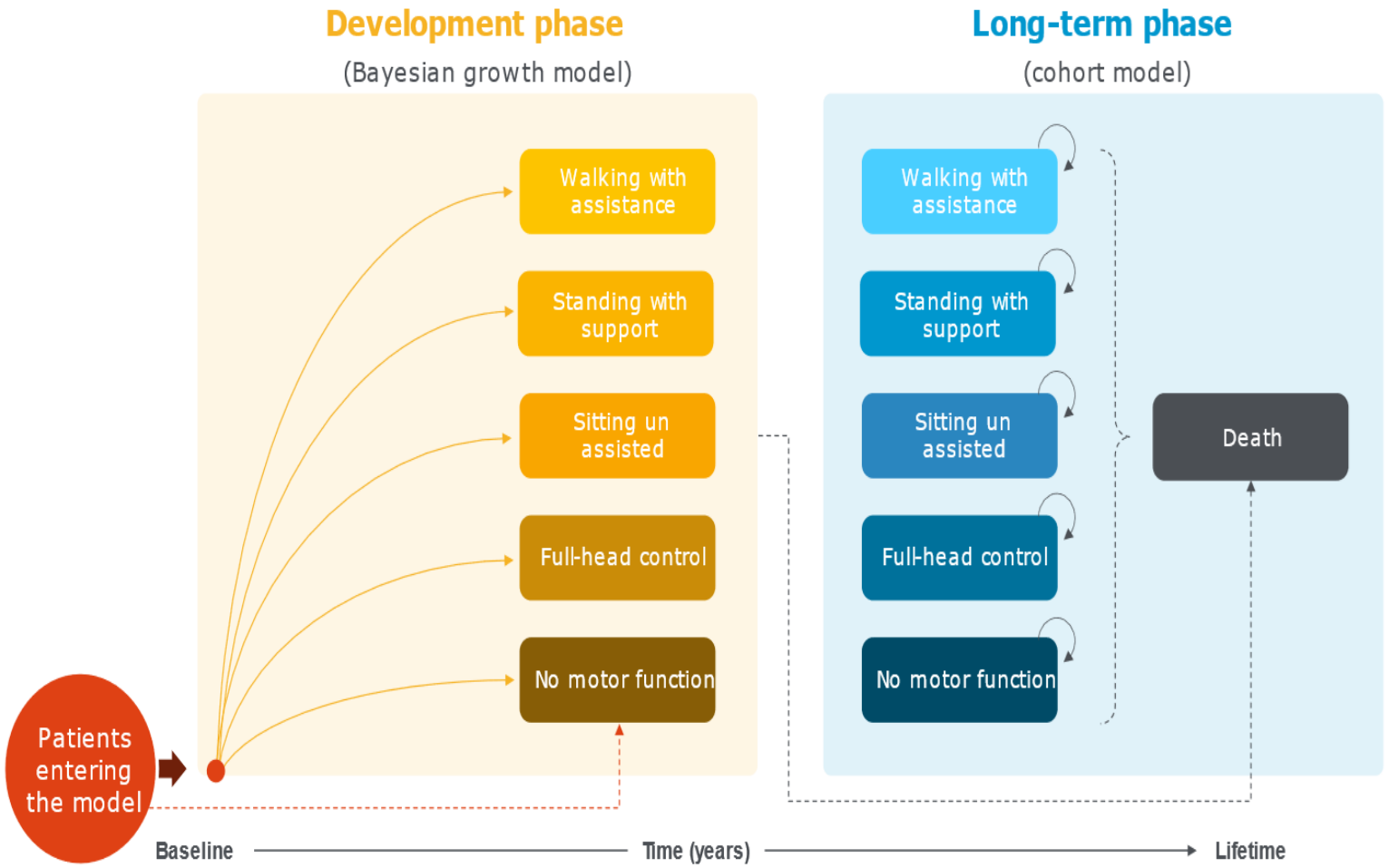
	No motor milestone		Full head alignment		Sitting		Stepping		Walking with assistance	
	BSC	EE	BSC	EE	BSC	EE	BSC	EE	BSC	EE
Baseline	49 (100%)	100%	0 (0%)	0%	0 (0%)	0%	0 (0%)	0%	0 (0%)	0%
Year 1	48 (98%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]	0 (0%)	[redacted]	0 (0%)	[redacted]
Year 2	47 (96%)	[redacted]	1 (2%)	[redacted]	0 (0%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]
Year 3	47 (96%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]
Year 4	47 (96%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]
Year 5 +	47 (96%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]	0 (0%)	[redacted]	1 (2%)	[redacted]

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Model structure informed by those used for spinal muscular atrophy



EAG comment:

- Model includes two phases:
  - short-term development phase (initial 12 years) where PDMS-2 scores predicted by Bayesian growth model, and
  - long-term phase (12 years to lifetime) driven by mortality.
- Appropriate that survival curves informed by study on patients with a proxy condition – cerebral palsy.
- Some concerns about company's preferred approach of using PDMS-2 scores to derive motor milestone health state.

PDMS-2, Peabody Developmental Motor Scales Second Edition

Company's model overview

Bayesian modelling to predict PDMS-2 scores

- Company fitted a Bayesian growth curve model to the observed individual PDMS-2 scores and extrapolated them up to 12 years (development phase of model).
- Only raw PDMS-2 scores from the clinical trials were used to estimate motor milestone; other outcomes were not used.
- Company fitted Bayesian regression models (asymptotic, logistic and Gompertz) as patients' progression towards achieving developmental milestones was assumed to eventually plateau (asymptote assumption).
- Gompertz distribution used in company base case, based on goodness of fit and clinical validation.
- Asymptotic model was used in scenario analysis, which reduces ICER for eladocagene exuparvovec vs best supportive care.

EAG comment:

- Agree Bayesian growth curve model is reasonable approach to analysis, provided asymptote assumption is appropriate.
- Agree choice of Gompertz model in company base case is reasonable.
- However, growth model is reliant on assumption that there is no deterioration of motor milestones.

PDMS-2, Peabody Developmental Motor Scales Second Edition

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	From AADC-010, AADC-011, and AADC-CU/1601 trials (EE)
Intervention efficacy	Motor milestone achievements based on individual patient-level PDMS-2 scores from the AADC-010, AADC-011, and AADC-CU/1601 trials
Comparator efficacy	Motor milestone achievements based on natural history database (NHDB)
Adverse events	Only moderate or severe TEAEs were included from the 3 EE trials. AEs not considered for BSC cohort due to lack of literature and evidence.
Utilities	No quality of life data from trials. Utilities derived from time trade off method using vignettes created for each motor milestone health state.
Resource use	Assumed that resource use values associated with each motor milestone health state differ, based on clinical expert opinion.

EAG comment:

- Data used in the model is from a February 2020 data cut.
- More long-term data (narrative form) was provided at clarification stage, from a January 2022 data cut.
- Additional ad-hoc analysis was provided at technical engagement, from an August 2022 data cut.

EE, eladocagene exuparvovec; BSC, best supportive care; TEAEs, treatment-emergent adverse events; AEs, adverse events

Key issue: How observed trial data on motor milestone achievement was derived

Background

- EAG could not check accuracy of pooled proportions of participants from each trial achieving the motor milestones used in a company economic model scenario analysis and in EAG's base case.

Company

- Provided additional information at technical engagement to justify approach to pooled data and explain missing/imputed data.
- Confirms its view that all options for modelling motor milestones based on observed trial data are limited due to the diminishing number of patients providing data in the model over time. More appropriate to predict motor milestone attainment from PDMS-2 total score.

EAG comments

- Clarification from company at technical engagement on number of participants included in observed trial data used in economic model is helpful.
- Still unclear how model estimates for last observation carried forward (LOCF) approach were derived as underlying numerators are not clearly reported.

Does the additional information provided by the company at TE address EAG uncertainty?

Key issue: Use of PDMS-2 scores to predict motor milestone achievement (1)

Background

- Company uses a Bayesian growth curve model using PDMS-2 scores to predict motor milestone development up to 12 years. EAG has concerns that this potentially overestimates the effectiveness of eladocagene exuparvovec, when compared with observed distribution from pooled trials.

Company

- Strongly believes using PDMS-2 total scores to predict motor milestones is preferable to using observed trial motor milestone achievements, because:

(i) Predicting motor milestones based on PDMS-2 allows for future motor milestone attainment
(ii) PDMS-2 is a well-validated measure of motor function that is sensitive to small changes over time
(iii) PDMS-2 scores provide a more complete picture of treatment effect than motor milestone alone.

EAG comments

- Still prefer use of observed trial data (with LOCF approach to impute missing data).
- More recent data beyond 60 months should be included in economic model to lessen uncertainty.
- Exploratory scenario shortening length of developmental phase of the model from 12 to 5 years shows a small impact on the ICER (i.e. effect of company's Bayesian growth model on development beyond 5 years is minimal).

NICE

PDMS-2, Peabody Developmental Motor Scales Second Edition; LOCF, last observation carried forward

Key issue: Use of PDMS-2 scores to predict motor milestone achievement (2)

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 for EE arm

	No motor milestone		Full head control		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]

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

Does committee agree with EAG objections to use of PDMS-2 scores to predict motor milestone achievement?

NICE

PDMS-2, Peabody Developmental Motor Scales Second Edition; EE, eladocagene exuparvovec

Key issue: Appropriateness of using LOCF approach for estimating missing data in the pooled analysis (1)

Background

- EAG base case uses the last observation carried forward (LOCF) approach to estimating missing data in pooled analysis. Company argue this approach is inappropriate.

Company

- Predicting based on PDMS-2 total score is most appropriate approach: assumes people with limited follow-up data can achieve motor milestones in future, whereas LOCF approach does not allow for future motor milestone achievement, which is clinically implausible.
- Fluctuations in PDMS-2 scores following treatment with eladocagene exuparvovec, do not indicate a reduction in treatment effect or a change in motor milestone attainment. Instead, evidence suggests these are driven by external factors (e.g. injuries, illness) and test fatigue (e.g. tiredness, and lack of motivation).

EAG comments

- Agree appropriate to assume no decline in motor milestone achievements over time, which supports assumptions within LOCF approach.
- Amount of missing data at each timepoint adds uncertainty to the cost-effectiveness estimates.

Which approach is more appropriate for estimating missing data: LOCF or estimates derived from PDMS-2 scores?

PDMS-2, Peabody Developmental Motor Scales Second Edition

Key issue: Appropriateness of using LOCF approach for estimating missing data in the pooled analysis (2)

Number of patients providing data at each timepoint (Feb 2020 data cut)

Time (months)	Patients with motor milestone data at each time point, % (N)
0 (Baseline)	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

EAG comments:

- This data, provided by the company at technical engagement, suggests a large proportion of missing data were imputed.
- This adds uncertainty to cost-effectiveness estimates, as large number of treatment outcomes were presumably imputed.
- Would have been preferable for company to have used more recent data in economic model.
- This would have reduced need for data imputation and resulted in less uncertainty in results.

Key issue: Uncertainty about longer-term efficacy of eladocagene exuparvovec between 5 and 10 years post-surgery

Background

- Lack of clarity on high attrition rates in long-term follow up of participants from 3 trials means that longer-term efficacy of eladocagene exuparvovec beyond five years is uncertain and at risk of bias.

Company

- Provided further details at technical engagement on long-term follow up data collection and participants who entered long-term follow up.
- Ad hoc analysis indicates there is unlikely to be bias in long-term follow-up data.
- Should be noted that not all participants had longer-term data at time of the February 2020 data cut used in the company model, because they had not yet reached first long-term follow-up visit.

EAG comments

- EAG agree that there is no selection or attrition bias in relation to long-term follow up data.
- Long-term data are not available for all enrolled participants, outcomes for these individuals are unknown.
- Uncertainty about longer-term efficacy of eladocagene exuparvovec remains.

Does additional information provided by company at TE resolve EAG concerns over possible risk of bias and uncertainty in the long term efficacy of EE?

Key issue: Uncertainty in the persistence of treatment benefit in the long term, over people's lifetimes

Background

- Company assumes treatment effect of eladocagene exuparvovec persists over patients' lifetime. This assumption is uncertain due to a lack of longer follow up data beyond 10 years post-surgery.

Company

- persistence of treatment benefit over a person's lifetime supported by clinical evidence, underlying biology and mechanism of action:

(i) eladocagene exuparvovec durably restores AADC enzyme functioning.
(ii) clinical trials showed sustained improvement in motor milestone achievement throughout follow-up.
(iii) company considers the EAG's treatment waning scenarios to be clinically unrealistic.

- EMA concluded not appropriate to assume decline of treatment effect over time for this technology.

EAG comments

- Agree improvements in motor function likely maintained over time due to restored AADC enzyme.
- A strength of the studies was that longer follow-up data between 5-10 years post-treatment for [redacted]% of the participants were collected ([redacted]), although a very small number had data available at exactly 10 years.
- Remains uncertain whether improvements will be maintained beyond 10 years post-surgery.

Is there any evidence to suggest that treatment waning scenarios are clinically plausible for eladocagene exuparvovec?

AADC, Aromatic L-amino acid decarboxylase; EMA, European Medicines Agency

Key issue: Survival extrapolation methods used by the company overestimate survival for “walking with assistance”

Background

- Company modelled survival based on motor milestone health states. Mortality data based on the proxy condition cerebral palsy was used to inform survival estimates for patients with AADC deficiency

Company

- For their base case, log-logistic curve was chosen for: no motor function; full head control; sitting unassisted; and standing with support, and exponential curve for walking with assistance.

EAG comments

- 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.
- At technical engagement company agreed with EAG’s preferred survival extrapolations: Weibull for all health states, except for “walking with assistance” (exponential).
- Using exponential curve overestimates survival of patients in the “walking with assistance” health state.
- Unclear whether the use of Weibull for “walking with assistance” is clinically plausible: survival is similar for patients in the “standing with support” health state beyond 45 years.
- Use of Weibull for this health state would have a considerable upwards impact on the final ICER.

Is it clinically plausible for survival in “walking with assistance” health state to be similar to survival in “standing with support” health state beyond 45 years?

Key issue: Discount rate used in company base case (1)

Company used a discount rate of 1.5% for costs and benefits

NICE process and methods manual:

4.5.3 The committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

4.5.4 When considering analyses using a 1.5% discount rate, the committee must take account of plausible long-term health benefits in its discussions. The committee will need to be confident that there is a highly plausible case for the maintenance of benefits over time when using a 1.5% discount rate.

Is the discounted rate of 1.5% appropriate for this appraisal?

Key issue: Discount rate used in company base case (2)

Company choice of 1.5% has big impact on cost-effectiveness

Background

- Use of 1.5% discount rate based on NICE criteria: 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.

Company

- Strongly believes technology meets criteria for 1.5% discount rate which was intended to cover situations similar to this (costs incurred upfront, but benefits accrued over longer period).
- A need to consider appropriate definition of "full or near-full health" in the context of AADC deficiency and this appraisal. Treatment is transformative and health-restoring.
- Current biologic, clinical, and expert evidence highlights that benefits likely sustained long-term.
- Considers this appraisal to be similar to HST15 (onasemnogene abeparvovec), where 1.5% accepted

EAG comments

- Agree that 1.5% discount rate was accepted for a similar previous NICE appraisal (HST 15).
- EAG clinical expert considered that "full or near-full health" would not be achieved.
- EAG believe this issue would benefit from further discussion with other clinical experts.
- Did scenario analyses with different discount rates.

Is the discounted rate of 1.5% appropriate for this appraisal?

Summary of company and EAG base case assumptions

Assumption	EAG base case	Updated company base case (post-TE)
Baseline age and weight	6 years and 15 kg	4 years and 11.1 kg (means from trials)
Discount rate of costs and effects	3.5% (present results for both 1.5% and 3.5%)	1.5%
Motor milestone achievement (EE)	Trial observed distribution of patients across motor milestone health states using the LOCF approach to impute missing data	Bayesian growth curve model using PDMS-2 scores to predict motor milestone development
Adverse events	Occurring in ≥5% of people	Accept EAG approach
Extrapolation of survival curves	Weibull curve to extrapolate survival in all health states, except for "walking with assistance" (exponential)	Accept EAG approach
Costs	All costs updated to 2021/2022 prices	Accept EAG approach
Resource use estimates	Informed by the EAG's clinical expert	Accept EAG approach
Number of carers	Most severe health state (no motor function) requires 2.5 carers while other health states require 2 carers.	Accept EAG approach

- At technical engagement company accepted many of EAG's preferred assumptions.

Decision modifiers for highly specialised technologies

NICE process and methods manual:

6.2.23 For highly specialised technologies, the committee will consider the size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of the technology to fall within the highly specialised technologies £100,000 cost per QALY level.

6.2.24 For this weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained.

Incremental QALYs gained	Weight
Less than or equal to 10	1
11 - 29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

- When undiscounted QALY gain is between 11 - 29, modifier is calculated by dividing QALY gain by 10.

Company base case results

Deterministic incremental base case results (discounted at 1.5%, QALY modifier applied, PAS price)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Undiscounted QALY gain is [redacted], so QALY modifier of [redacted] applied in the company base case ICER.

Total costs, QALYs and ICER from the PSA, PAS price

	Total costs (95% CI)	Total QALYs (95% CI)	ICER (95% CI)
BSC	[redacted]	[redacted]	[redacted]
Eladocagene exuparvovec	[redacted]	[redacted]	[redacted]

NICE

LYG, life years gained; QALY, quality-adjusted life year; CI, confidence interval; ICER incremental cost-effectiveness ratio

Company deterministic scenario analysis

Base case setting	Scenario explored	Incremental costs	Incr. QALYs	ICER
Base case	-	[redacted]	[redacted]	[redacted]
QALY modifier applied	QALY modifier not applied	[redacted]	[redacted]	[redacted]
Population: 4 years, 11.1kg	Population: 2 years, 8.5kg	[redacted]	[redacted]	[redacted]
	Population: 6 years, 15kg	[redacted]	[redacted]	[redacted]
Discount rate - QALYs: 1.5%, costs: 1.5%	QALYs: 3.5%, costs: 3.5%	[redacted]	[redacted]	[redacted]
	QALYs: 0%, costs: 0%	[redacted]	[redacted]	[redacted]
Model specification: Gompertz (28 patients)	Model specification: Asymptotic (28 patients)	[redacted]	[redacted]	[redacted]
Length of developmental phase: 12 years	Length of developmental phase: 9 years	[redacted]	[redacted]	[redacted]
Modelling motor milestones through Bayesian growth model	Modelling motor milestones though observed distribution (LOCF approach)	[redacted]	[redacted]	[redacted]
	Modelling motor milestones though observed distribution (distribution per follow-up)	[redacted]	[redacted]	[redacted]
Development based on NHDB	NHDB-based development: No improvement for patients on BSC	[redacted]	[redacted]	[redacted]
	NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]	[redacted]	[redacted]

EAG base case results, pre-technical engagement (1)

EAG's preferred model assumptions (QALY modifier applied, PAS price)

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER (£/QALY)	
		3.5%	3.5%	3.5%	1.5%
EAG corrected company base case*	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
+ Age and weight: 6 years and 15kg	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
+ Motor milestone achievement: observed data (LOCF)	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
+ Adverse events: ≥5%	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
+ Extrapolation of survival: Weibull + exponential	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
+ Updated costs	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]

* EAG corrected some minor errors in parameter inputs and coding.

EAG base case results, pre-technical engagement (2)

EAG's preferred model assumptions (cont.)

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER (£/QALY)	
		3.5%	3.5%	3.5%	1.5%
+ Resource use estimates: EAG expert	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
+ Number of carers: 2.5 for no motor function and 2 for the other health states	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred base case	BSC	[redacted]	[redacted]	[redacted]	[redacted]
	EE	[redacted]	[redacted]	[redacted]	[redacted]

EAG preferred base case, post-technical engagement:

- Based on conversations with the company at technical engagement, cost of paediatric intensive care unit stay and ward stay were revised in the EAG base case.
- This changes the EAG base case ICER from [redacted] to [redacted] for 1.5% discount rate, and from [redacted] to [redacted] for 3.5% discount rate.

EAG deterministic scenario analysis, pre-technical engagement

EAG scenario analyses (deterministic)

Scenario	ICER (£/QALY)	
	1.5%	3.5%
EAG preferred model	[redacted]	[redacted]
QALY modifier not applied	[redacted]	[redacted]
Bayesian growth model: Asymptotic (28 patients)	[redacted]	[redacted]
NHDB-based development: No improvement for patients on BSC	[redacted]	[redacted]
NHDB-based development: Improvement in motor milestone achievement for BSC patients: 2% per year (instead of using NHDB)	[redacted]	[redacted]
Survival: Weibull for all health states	[redacted]	[redacted]

Other considerations

Equality considerations

- No equality considerations have been raised in relation to the technology.

Innovation

- As the first gene replacement therapy for patients with AADC deficiency and the first disease-modifying option, eladocagene exuparvovec is a significant innovation and step-change in the optimal management of patients with AADC deficiency. It will be the first licensed treatment that addresses an underlying biological cause of this severe and life-limiting disease. Through a one-time administration, eladocagene exuparvovec is expected to provide transformative, life-changing benefits to patients and their families.

NICE National Institute for Health and Care Excellence

Thank you.