EE655

Cost-effectiveness analysis of eladocagene exuparvovec for the treatment of aromatic L-amino acid decarboxylase deficiency (AADCd) from a United States (US) perspective

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1. Background & Objectives:

AADCd is a rare, infantile-onset, neurometabolic disorder.

Characterized by motor dysfunction and developmental delays.[1]

Because of their condition, patients require care throughout their lifetime. There is a high probability of mortality in the first decade of life.[1,2]

Prior to the approval of the gene therapy eladocagene exuparvovec by the European Medicines Agency and Medicines and Healthcare products Regulatory Agency in 2022 for patients 18 months and older, there were no approved therapies for patients with AADCd.[3,4] Standard of care treatments have historically been aimed at symptom relief, and have not been associated with achievement of developmental milestones / motor function.[5]

Eladocagene exuparvovec, a one-time treatment recently granted Priority Review by the US Food and Drug Administration, is a recombinant adeno-associated virus serotype 2 (rAAV2) vector containing the human DDC gene that encodes the aromatic L-amino acid decarboxylase enzyme (hAADC) and compendial excipients.[5]

Clinical trials of eladocagene exuparvovec have shown meaningful improvements in motor function as measured by Total Peabody Developmental Motor Scales-Second Edition (PDMS-2) score,[6] as well as other measures of motor function.

Given the substantial clinical burden of the disease, the improvements resulting from treatment with eladocagene exuparvovec serve to address an unmet medical need.

New evidence has emerged since the publication of UK-perspective cost-effectiveness model for eladocagene exuparvovec,[7] including an analysis of health-related quality of life (HRQoL) by motor milestone state,[8] longer term clinical trial data, and derivation of a meaningful score difference (MSD) for Total PDMS-2 score.[9]

In this study, a cost-effectiveness analysis was conducted using the latest evidence and a multi-state modeling approach to compare eladocagene exuparvovec to best supportive care (BSC) for the treatment of patients with AADCd, from a US perspective.

2. Methods:

Data source

- Patient data (n=30) from 3 single-arm, open-label trials of eladocagene exuparvovec served as inputs for the models (data cut-off: June 2023).
- Health state utilities were from a US time-trade-off study valuing the quality-of-life impact of AADCd by motor milestone state (**Table 1**).[8]
  - The impacts on patients of variation in motor function in AADCd were described across five motor-milestone state "vignettes", which were validated by N=5 healthcare professionals with experience managing AADCd and N=4 caregivers of patients.
  - Time-trade-off assessment of the quality-of-life variation between the states was then assessed by an n=120 general-population sample in the US.

Approach 1: Multi-state modeling using MSD of Total PDMS-2

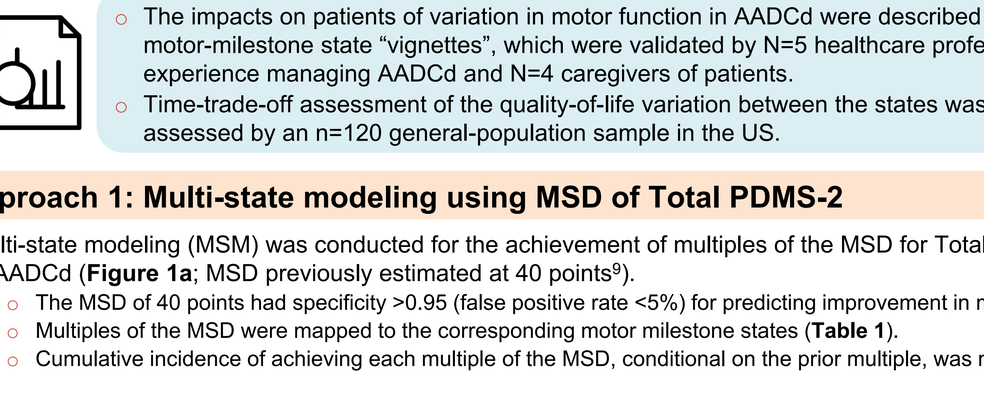
- Multi-state modeling (MSM) was conducted for the achievement of multiples of the MSD for Total PDMS-2 score in AADCd (**Figure 1a**; MSD previously estimated at 40 points[9]).
  - The MSD of 40 points had specificity >0.95 (false positive rate <5%) for predicting improvement in motor milestones.
  - Multiples of the MSD were mapped to the corresponding motor milestone states (**Table 1**).
  - Cumulative incidence of achieving each multiple of the MSD, conditional on the prior multiple, was modeled.

Table 1. Multiples of meaningful score difference and utilities for motor milestones in AADCd

Motor milestone	Multiples of MSD for Total PDMS-2*	Utilities[8]
No motor function (NMF)	0	-0.258
Full head control (FHC)	1 (40 pts)	-0.155
Sitting unassisted (SU)	2 (80 pts)	0.452
Standing with support (SWS)	3 (120 pts)	0.775
Walking with assistance (WWA)	4 (160 pts)	0.796

*Meaningful score difference was derived from an analysis of data from patients (n=30) from three single-arm clinical studies of eladocagene exuparvovec. An MSD of 40 points yielded specificity >0.95 using the receiver operating characteristic approach, and generally aligned with the mean-difference approach.[9]
Note: All patients started from the "no motor function (NMF)" state.

Figure 1. Patient distribution throughout CEA development phase



Approach 2: Multi-state modeling using motor milestone achievement

- An alternative approach modeled cumulative incidence of motor milestone achievement (**Figure 1b**).
  - Motor milestone achievement was observed over ≥2 years for 26 (87%), and ≥5 years for 19 (63%).†

†For patients with relatively shorter follow-up, the probability of achieving future motor milestones was informed by their highest motor milestone achieved at time of censoring, and the cumulative incidence of achieving each higher motor milestone among patients with longer follow-up (conditional on the milestone at time of censoring).

For both approaches:

- Patient age at baseline was modeled as 4 years (clinical studies mean).
- A development phase lasting 12 years was modeled (to include up to 132 months of follow-up from clinical studies), during which motor milestones could be achieved.
- Motor milestone (MM) achievement was held constant during the long-term phase of the model (i.e., from age 16 years on).

3. Results:

Patient characteristics

Data from **30 patients** were analyzed

87% had follow-up ≥2 years

53.3% were male

Mean (SD) age at initiation of eladocagene exuparvovec was **45.7 (26.2)** months

LY and QALY results

Multi-state modeling based on multiples of the Total PDMS-2 MSD indicated incremental (i.e., difference of eladocagene exuparvovec vs. BSC) life-year (LY) gains of **36.00** and quality-adjusted life-year (QALY) gains of **40.10**.

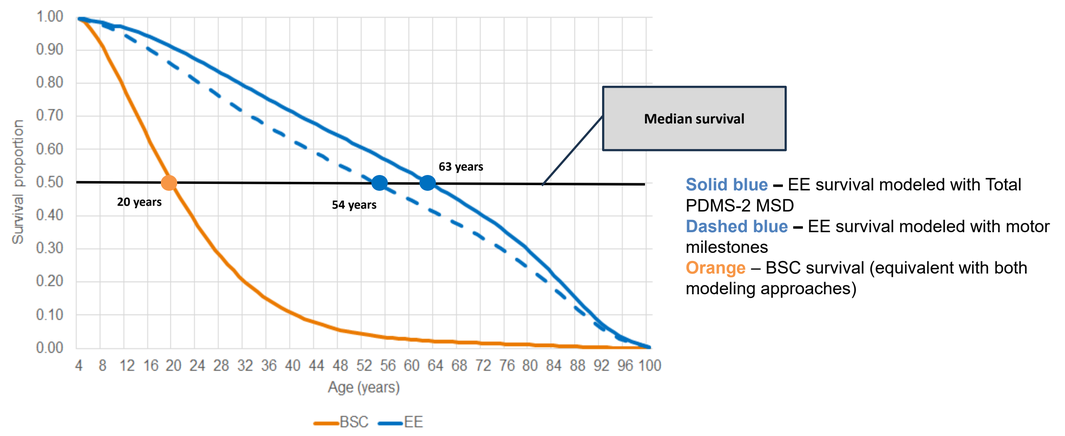
Modeling motor milestone achievement, incremental LY gains were **30.55** and QALY gains were **34.84.**

Table 2. Summary of CEA results

	LYs, undiscounted			QALYs, undiscounted		
Model	**EE**	**BSC**	**Incremental**	**EE**	**BSC**	**Incremental**
MSM using MSD of Total PDMS-2	54.71	18.71	**36.00**	33.85	-6.25	**40.10**
MSM using MM achievement	49.26	18.71	**30.55**	28.59	-6.25	**34.84**

BSC, best supportive care; CEA, cost-effectiveness analysis; EE, eladocagene exuparvovec; LYs, life years; MSM, multi-state modeling; QALYs, quality-adjusted life-years
Note: Background mortality was modeled based on US life tables, and mortality risk associated with motor milestone health states informed by an analog condition, cerebral palsy.[10].

Figure 2. Overall survival



Modeling of overall survival showed marked **improvement in median survival** with eladocagene exuparvovec over BSC (20 years) both with the motor milestone (54 years) and Total PDMS-2 MSD (63 years) approaches.

4. Discussion & Conclusions:

This study evaluated the cost-effectiveness of eladocagene exuparvovec compared to best supportive care (BSC) for the treatment of patients with AADCd from a US perspective.

Of the two approaches, using multiples of MSD for Total PDMS-2 score to define health states provides greater sensitivity in measuring improvements because it captures a broad range of both gross and fine motor domains.

Note that, in common with other ultra rare diseases, the limited availability of long-term natural history data (including survival data) in AADCd is a challenge for economic modeling. Based on expert recommendation, cerebral palsy survival data has been used as an analog and the incremental LYs across the two approaches reflect the differences in mortality risk modeled by health state, based on that data.

Both approaches showed substantial improvement in overall survival with eladocagene exuparvovec, particularly as the BSC overall survival estimate used in the model may be considered conservative.[11]

It is notable that when discounted at 3%, the incremental QALYs of eladocagene exuparvovec were found to be relatively higher than estimates reported for onasemnogene abeparvovec gene therapy for spinal muscular atrophy,[12,13] a treatment that has had positive reimbursement outcomes.[14]

A limitation of the study was the potential for inaccuracy in the calculation of time at motor milestone achievement, as this was modeled as the minimum of visit months when the relevant motor milestone was reported to be achieved. Given the observation intervals, achievement of the motor milestone may have occurred earlier.

Strengths of this study include consistent findings across alternative approaches, utilization of long-term follow-up data, more responsive measure of motor-function improvement provided by Total PDMS-2 MSD than a 5-point motor-milestone scale[9] and utility data used was based on updated vignettes (incorporating feedback from both clinicians and caregivers) and valuated by a US general-population sample.[8]

This study suggests that patients have significant LY and QALY gains with eladocagene exuparvovec treatment compared to BSC, indicating that eladocagene exuparvovec is a transformative treatment for AADCd.

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