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Improvements in the Peabody Developmental Motor Scale, Second Edition (PDMS-2) and correlation with Bayley-III scores and motor milestones in aromatic L-amino acid decarboxylase deficiency (AADCd)

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1. Background & Objectives:

- AADCd is a rare, autosomal recessive, neurometabolic disorder of monoamine neurotransmitter synthesis.
- Deficiency of the AADC enzyme hinders the synthesis of dopamine and serotonin from their precursors. Without neuronal dopamine, patients experience movement disorders, as well as behavioral problems, autonomic dysfunction, and developmental delay.[1-3]
- Disease onset is typically during the first months of life, with most patients presenting a severe phenotype characterized by early-onset hypokinesia, dystonia, and oculogyric crises.[2]
- Patients with AADCd generally have minimal functional motor movement and very rarely reach developmental milestones.[4]
- The gene therapy eladocagene exuparvovec has been developed for the treatment of patients with AADCd, and marketing authorization was granted in EU and UK in 2022, based on positive recommendations from the European Medicines Agency (EMA)[7] in July 2022 and United Kingdom's Medicines and Healthcare products Regulatory Authority (MHRA) in November 2022.[8]
- Clinical trials of eladocagene exuparvovec have assessed changes in patients' motor function using PDMS-2 and changes in cognitive development using Bayley-III.
  - The PDMS-2 is a tool for assessing motor function and has been validated for use in young children (aged 0 to 5).[5,9] It consists of 6 subtests comprising 249 items, which are scored on a 0-2 scale, for 498 total possible points. In eladocagene exuparvovec studies, the "Reflexes" subtest (8 items, 16 total possible points) was not assessed, such that total scores possible range from 0-482.[5,9-11]
  - The Bayley-III is a standardized instrument used to assess neurodevelopment among young children, and could identify developmental delays, including non-motor (cognitive, social/emotional) delays.[6]
- To determine thresholds that identify when individual patients have experienced meaningful improvement in measure scores, the US FDA recommends the use of a meaningful score difference (MSD) estimation in descriptive analyses.[12]

This study characterized the MSD of PDMS-2 and correlations with Bayley-III and motor milestones.

2. Methods:

Data source

- Data as of July 2022 from three single-arm, open-label clinical studies that investigated eladocagene exuparvovec for the treatment of patients with AADCd were analyzed:
  - Compassionate use study, Phase 1/2 trial (NCT01395641), Phase 2b trial (NCT02926066)[13]
  - All studies were conducted at the National Taiwan University Hospital

Key inclusion criteria
❑ Confirmed diagnosis of AADCd: cerebrospinal fluid analysis to show reduced levels of neurotransmitter metabolites (homovanillate and 5-hydroxyindole acetic acid) and higher levodopa, together with ≥1 mutation within AADC gene
❑ Classical clinical characteristics of AADCd: oculogyric crises, hypotonia, developmental retardation
❑ ≥2 years of age or having a head circumference big enough for surgery
Key exclusion criteria
❑ Significant brain structure abnormality

- Pre- and post-treatment outcomes that were assessed in this analysis were:
  - Total PDMS-2 and gross motor domain score
  - Bayley-III cognition and language domain scores
  - Motor milestones achievement

Analysis

MSD estimation:

- As recommended by the US FDA guidelines,[12] the MSD for improvement in Total PDMS-2 score was estimated by anchoring against clinically meaningful disease progression endpoints (i.e., improvement in motor milestones: head control, sitting unassisted, standing with support, walking with assistance; milestone achievement was determined based on emergence or mastery of the milestone)
- Meaningful differences on the anchor were mapped onto differences in the Total PDMS-2 score
- Mean-difference and receiver operating characteristic (ROC) curve approaches were used

Correlations:

- Correlations were calculated between the following:

❑ Change from baseline (CFB) in Total PDMS-2 vs. Bayley-III score comprising cognition & language domains
❑ CFB in Total PDMS-2 vs. motor milestones achieved by age group (≤4 years; >4 years)
❑ CFB in PDMS-2 gross motor domain score vs motor milestones achieved by age group (≤4 years; >4 years)
❑ CFB in Total PDMS-2 vs. Bayley-III cognition domain score
❑ CFB in Total PDMS-2 vs. Bayley-III language domain score

4. Discussion & Conclusions:

- In clinical trials, AADCd patients treated with eladocagene exuparvovec experienced meaningful improvements in motor function, reflected by significant improvements in Total PDMS-2 score.
- MSD of 40 points for Total PDMS-2 may help interpretation of improvements observed in eladocagene exuparvovec clinical studies.
- By capturing both gross and fine motor domains, the PDMS-2 MSD provides greater sensitivity in measuring improvements. These improvements may be notable as early as six months following treatment, before improvements are observed in motor milestones.
- Significant correlations between CFB in Total PDMS-2 and Bayley-III cognition and receptive communication domain scores suggest that in AADCd, motor function improvements measured with PDMS-2 may be associated with improvements in other domains (including non-motor domains).
- As the PDMS-2 and motor milestones both assess gross motor skills, a high degree of correlation is expected. The lower correlation observed with expressive communication is likely a result of the later attainment of these skills in the course of childhood development.
- While the PDMS-2 has only been validated for children aged 0 to 5 years, correlations between CFB in Total PDMS-2 score and motor milestone achievement were consistent and significant for both the age ≥4 and <4 years groups. This was also observed with CFB in PDMS-2 gross motor domain score and motor milestone achievement.

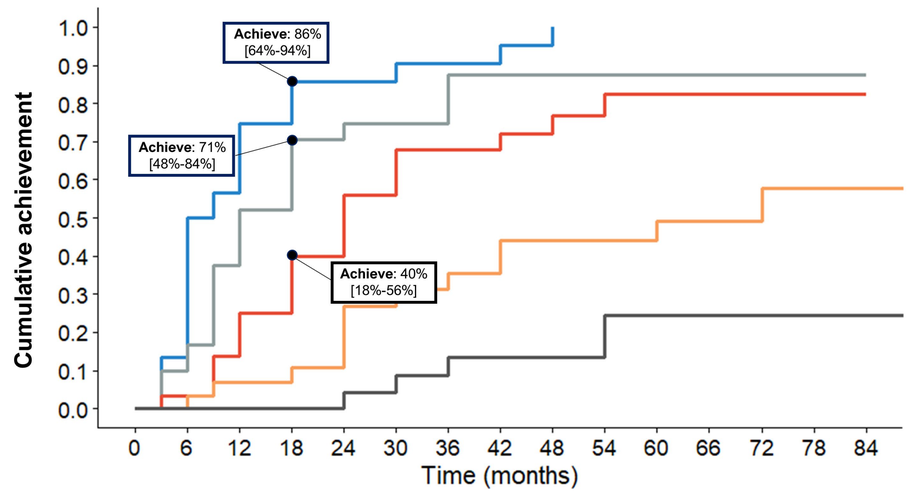
Taken together, these findings suggest that for patients with AADCd, treatment with eladocagene exuparvovec leads to significant improvements in motor function as well as cognitive and social function.

3. Results:

MSD estimation

- Data from 30 patients with AADCd were analyzed, with a median follow-up of 60 months
- Mean (standard deviation [SD]) age at initiation of eladocagene exuparvovec was 45.7 (26.2) months; 53.3% were male
- MSD of Total PDMS-2 score was 45 points using the mean-difference approach, and 30-40 points using the ROC approach and maximizing specificity (minimizing false signals of improvement)
  - An MSD of 40 for Total PDMS-2 score was used for the analysis as it yielded specificity >0.95 (false positive rate <5%) using the ROC approach and generally aligned with the estimate from the mean-difference approach
- Following eladocagene exuparvovec treatment, 50% of patients had achieved the MSD of 40-point change in Total PDMS-2 score at 6 months, and 86% at 18 months (**Figure 1**). At the 18-month timepoint, 71% of patients had achieved head control and 40% were sitting unassisted

Figure 1. Proportion of patients achieving 40-point Total PDMS-2 score compared to proportion achieving motor milestones over time, following eladocagene exuparvovec treatment



% (95% CI) of patients achieving MSD of Total PDMS-2 score or motor milestones

	Month 0	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 66	Month 72	Month 78	Month 84
40pts Total PDMS-2 change	0 (0, 0)	50 (28, 65)	75 (53, 87)	86 (65, 94)	86 (65, 94)	90 (68, 97)	90 (68, 97)	95 (70, 99)	100 (70, 99)	100 (70, 99)	100 (70, 99)	100 (70, 99)	100 (70, 99)	100 (70, 99)	100 (70, 99)
Head control	0 (0, 0)	17 (2.2, 29)	52 (30, 67)	71 (48, 84)	75 (52, 87)	75 (52, 87)	87 (65, 96)	87 (65, 96)	87 (65, 96)	87 (65, 96)	87 (65, 96)	87 (65, 96)	87 (65, 96)	87 (65, 96)	87 (65, 96)
Sitting unassisted	0 (0, 0)	3.3 (0, 9.5)	25 (7.0, 39)	40 (18, 56)	56 (32, 71)	68 (44, 82)	68 (44, 82)	72 (48, 85)	77 (52, 89)	82 (56, 93)	82 (56, 93)	82 (56, 93)	82 (56, 93)	82 (56, 93)	82 (56, 93)
Standing with support	0 (0, 0)	3.3 (0, 9.5)	6.8 (0, 15)	11 (0, 21)	27 (7.5, 42)	31 (10, 47)	36 (14, 52)	44 (20, 61)	44 (20, 61)	44 (20, 61)	49 (24, 66)	49 (24, 66)	58 (28, 75)	58 (28, 75)	58 (28, 75)
Walking with assistance	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	4.2 (0, 12)	8.7 (0, 20)	14 (0, 27)	14 (0, 27)	14 (0, 27)	24 (3.0, 41)	24 (3.0, 41)	24 (3.0, 41)	24 (3.0, 41)	24 (3.0, 41)	24 (3.0, 41)

Abbreviations: CI, confidence interval; MSD, meaningful score difference; PDMS-2, Peabody Developmental Motor Scale, Second Edition

Correlations

- Correlations between CFB in Total PDMS-2 and CFB in Bayley-III scores (cognition and language domains) improved over time; notably, these were of large magnitude and significant from Month 6 onwards (**Table 1**)
- At Month 6: r=0.599, p=0.0032; Month 18: r=0.796, p=0.0002; Month 60: r=0.861, p=0.0007
- When examined by subtest (**Table 1**):
  - CFB in Total PDMS-2 vs. CFB in Bayley-III cognition subtest score: significance was achieved by 6 months (r=0.637, p=0.0014)
  - CFB in Total PDMS-2 vs. CFB in Bayley-III language subtests: significance in the receptive communication subtest was achieved at 30 months (r=0.523, p=0.0376); in the expressive communication subtest, while the correlation improved over time, significance was not reached
- Correlations between improvements in motor milestones and CFB in Total PDMS-2 were significant both for patients aged ≥4 (r=0.934, p<0.0001) and <4 years (r=0.892, p<0.0001)
- When looking at correlations between improvements in motor milestones and the CFB in PDMS-2 gross motor domain scores only, these correlations remained significant (patients aged ≥4: r=0.904, p<0.0001; patients aged <4 years: r=0.958, p<0.0001)

Table 1. Correlation coefficients between CFB Total PDMS-2 and Bayley-III (cognition and language domains) scores over time

		Both cognition & language domains		Cognition subtest only		Receptive communication subtest only		Expressive communication subtest only	
Timepoint	n	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
Month 3	22	0.251	0.2606	0.372	0.0878	0.135	0.5485	-0.277	0.2125
Month 6	22	0.599	**0.0032**	0.637	**0.0014**	0.210	0.3472	-0.132	0.5589
Month 9	20	0.735	**0.0002**	0.808	**<0.0001**	0.223	0.3438	0.147	0.5353
Month 12	19	0.769	**0.0001**	0.858	**<0.0001**	0.243	0.3156	0.141	0.5659
Month 18	16	0.796	**0.0002**	0.881	**<0.0001**	0.314	0.2361	0.261	0.3288
Month 24	18	0.788	**0.0001**	0.923	**<0.0001**	0.416	0.0862	0.309	0.2114
Month 30	16	0.847	**<0.0001**	0.953	**<0.0001**	0.523	**0.0376**	0.380	0.1468
Month 36	14	0.767	**0.0014**	0.945[a]	**<0.0001**	0.730	**0.0030**	0.448	0.1084
Month 42	13	0.632	**0.0205**	0.958[b]	**<0.0001**	0.716	**0.0059**	0.413	0.1603
Month 48	13	0.795	**0.0012**	0.926	**<0.0001**	0.678	**0.0109**	0.299	0.3212
Month 54	10	0.834	**0.0027**	0.943	**<0.0001**	0.757	**0.0113**	0.416	0.2315
Month 60	11	0.861	**0.0007**	0.959	**<0.0001**	0.727	**0.0113**	0.471	0.1441
Month 72	6	0.972	**0.0012**	0.979	**0.0006**	0.836	0.0775[c]	0.593	0.2143
Month 84	4	0.997	**0.0028**	0.979	**0.0210**	0.942	0.0584	0.825	0.1747

[a] n=13; [b] n=12; [c] n=5
Abbreviations: CFB, change from baseline; n, number of patients; PDMS-2, Peabody Developmental Motor Scale, Second Edition

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