Request for ICD-10-PCS Code for Eladocagene Exuparvovec

ICD-10 Coordination and Maintenance Meeting

September 10, 2019

Baltimore, MD

AADC deficiency is a rare, terminal, inherited disorder of neurotransmitter synthesis[1]

Aromatic L-amino acid decarboxylase (AADC) deficiency is an inborn error of neurotransmitter biosynthesis, with an autosomal-recessive inheritance resulting from pathogenic mutations (>79 identified) in the dopamine decarboxylase gene (DDC) encoding for the AADC enzyme[2]

Lack of the AADC enzyme leads to a severe combined deficiency of dopamine, serotonin, and other catecholamines (norepinephrine and epinephrine) [1,3]

Key clinical symptoms include hypotonia, movement disorders, severe neurologic dysfunction, failure to achieve any developmental milestones, failure to thrive, and autonomic symptoms [1,3]

Patients with the most common phenotype of AADC deficiency have no functional motor movement, will never meet developmental milestones, and are at risk of an early death in the first decade of life[3,4]

AADC, aromatic L-amino acid decarboxylase; DDC, dopamine decarboxylase.

1. Wassenberg T, et al. *Orphanet J Rare Dis*. 2017;12(1):12. doi: 10.1186/s13023-016-0522-z.
2. Himmelreich N, et al. *Mol Genet Metab.* 2019 Mar 27. pii: S1096-7192(18)30786-8.
3. Hwu WL, et al. *J Inherit Metab Dis Rep.* 2018;40:1-6. doi: 10.1007/8904_2017_54.
4. Hwu WL, et al. *Sci Transl Med*. 2012;4(134):134ra161.

Symptoms of AADC deficiency have been identified as early as 3 months; however, the median age of diagnosis is 3.5 years[10]

Disease	Prevalence
Phenylketonuria	1:5,000–1:10,000[1]
Prader-Willi syndrome	1:16,000–1:25,000[a,2,3]
Pompe disease	1:28,000[a]–1:40,000[4]
AADC deficiency	1:32,000–1:90,000[5,6]
Spinal muscular atrophy	1:50,000–1:100,000[7]
West syndrome	1:100,000–1:900,000[8]
Segawa syndrome	1:200,000–1:1,000,000[9]

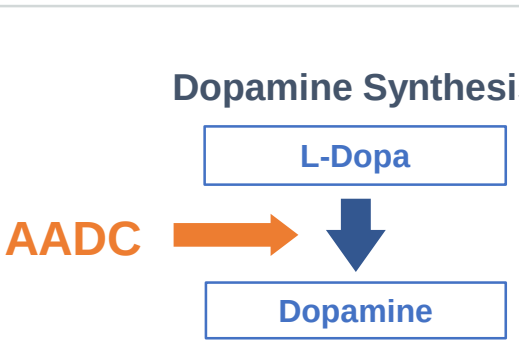
AADC, aromatic L-amino acid decarboxylase; DDC, dopamine decarboxylase.

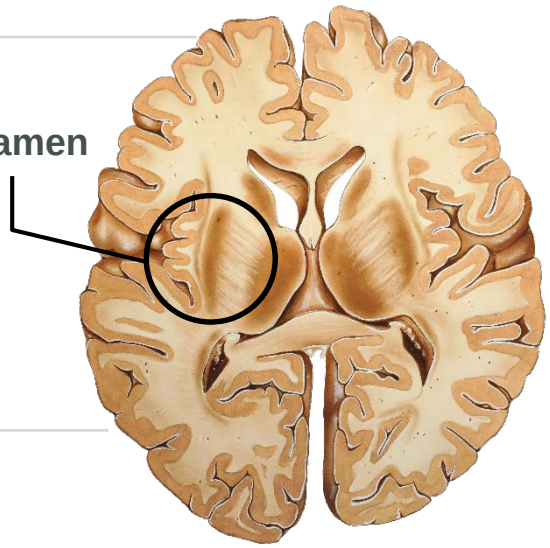
[a] Prevalence identified in US populations.

1. Phenylketonuria. Accessed July 3, 2018.
2. Burd L, et al. *Am J Med Genet.* 1990;37(1):97-99.
3. Butler MG. *Am J Med Genet.* 1990;35(3):319-332.
4. Dasouki M, et al. *Neurol Clin.* 2014;32(3):751-ix.
5. Hyland KR, Rheott M. [Manuscript in Progress.] 2018.
6. Chien YH, et al. *Mol Genet Metab.* 2016;118(4):259-263.
7. Verhaart IEC, et al. *Orphanet J Rare Dis.* 2017;12:124.
8. West syndrome. Accessed July 3, 2018.
9. Dopa-responsive dystonia. Accessed February 13, 2019.
10. Wassenberg T, et al. *Orphanet J Rare Dis*. 2017;12(1):12. doi: 10.1186/s13023-016-0522-z.

Loss of AADC activity leads to monoamine neurotransmitter deficiency[1]

- Mutation of the DDC gene causes deficiency of the AADC enzyme
- AADC makes dopamine via well-defined biochemical pathway





- ✓ Non-dividing cells
- ✓ Affected cells remain intact for long periods
- ✓ Limited, focal number of affected cells
- ✓ Amenable to direct delivery

AADC Deficiency Is a Well-Defined Monogenic Disorder Amenable to Gene Therapy

AADC, aromatic L-amino acid decarboxylase; DDC, dopamine decarboxylase; L-Dopa, levodopa.

1. Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12.

There are currently no FDA-approved drugs indicated for the treatment of AADC deficiency[1]

Pharmacologic Treatment[2,3]

First-Line Treatment	Dopamine receptor agonists	MAO inhibitors
Second-/ Third-Line Treatment	Anticholinergic agents	Benzodiazepines
Other Symptoms	AEDs (seizures)	Melatonin
	α-adrenoreceptor blockers	GI medications

Non-Pharmacotherapy[2,3]

Therapy	Physical
	Occupational
	Speech
Supplements	Folate
	Pyridoxine (vitamin B6)

Based on findings from the consensus guidelines, 99% of patients failed to achieve any motor milestones during their lifetime[2]

Current management options yield few improvements for the majority of patients with AADC deficiency[4]

AADC, aromatic L-amino acid decarboxylase; FDA, Food and Drug Administration; AED, antiepileptic drug; GI, gastrointestinal; MAO, monoamine oxidase.

1. Gene Therapy for the Treatment of AADC Deficiency. Accessed July 3, 2018.
2. Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12. doi: 10.1186/s13023-016-0522-z.
3. Data on File. 2018.
4. Chien YH, et al. *Lancet Child Adolesc Health.* 2017;1(4):265-273.

Eladocagene exuparvovec is the first targeted gene therapy designed to restore AADC function and dopamine synthesis in the putamen to improve patients' motor function and development[1]

PRODUCT PROFILE	DESCRIPTION OF ELADOCAGENE EXUPARVOVEC
Mechanism of Action	• Eladocagene exuparvovec is a gene therapy consisting of an AAV vector that delivers the human DDC gene to AADC-deficient cells in the CNS, resulting in increased production of the AADC enzyme and increase in the production of dopamine.
Product Administration	• Injected directly into the putamen, bilaterally with a single stereotactic surgery (~7–8 hours). • Supplied as a single-dose vial and injected with a dose volume of 80 µl per injection site (4 sites, 2 per putamen, total volume of 320 µl) at a total dose of 1.8 x 10^{11} vg per patient. • Surgery performed under general anesthesia, followed by a CT scan and MRI to check for acute bleeding and any structural changes. • Trajectories for intraputaminal infusion of eladocagene exuparvovec planned using fused MRI and CT images.
Patient Length of Hospital Stay	• Up to 3 to 4 days, in order to monitor patients for bleeding risk or surgical complications; dependent upon surgical/procedure protocol. • The administration of eladocagene exuparvovec is expected to be initially restricted to neurosurgeons at select centers of excellence.
New Technology	• There are currently no FDA-approved therapies to treat AADC deficiency. • No existing products have a similar mechanism of action and cannot be compared to any existing technology.

AADC, aromatic L-amino acid decarboxylase; AAV, adeno-associated virus; CNS, central nervous system; CT, computerized tomography; DDC, dopamine decarboxylase; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; vg, vector genomes.

1. Data on File. 2018.

Two clinical trials were performed for eladocagene exuparvovec (AADC-1601 and AADC-010)[1]

Objective	To determine if intraputaminal eladocagene exuparvovec administration can increase AADC activity and potentially improve motor function
Study Design	Two, single-arm, open-label clinical studies of eladocagene exuparvovec compared with natural history control
Natural History Control	82 patients with AADC deficiency and without developmental milestone achievement[2]
Subjects	Patients with AADC deficiency and without full head control, ability to sit, stand, or walk[3]
Interventions	All patients received a total dose of 1.8×10^{11} vg of eladocagene exuparvovec as bilateral intraputaminal stereotactic infusions during a single operative session

AADC, aromatic L-amino acid decarboxylase; vg, vector genomes.

1. Chien YH, et al. Poster presented at: The 6th International Symposium on Paediatric Movement Disorders, February 7-8, 2019; Barcelona, Spain
2. Wassenberg T, et al. *Orphanet J Rare Dis*. 2017;12(1):12. doi: 10.1186/s13023-016-0522-z.
3. Hwu WL, et al. *J Inherit Metab Dis Rep.* 2018;40:1-6. doi: 10.1007/8904_2017_54.

Clinical trial data for eladocagene exuparvovec will be available for 18 patients from AADC-1601 and AADC-010 at the time of filing[1]

Demographics	Diagnosis	Disposition[a]
18 patients were enrolled in studies AADC-1601 and AADC-010	At baseline, all patients had AADC deficiency[2,3]	Results for 8 patients are currently available at 5 years post-gene therapy
• **Age[b]:** 21 months to 8.5 years • **Gender:** 10 girls and 8 boys • **Race:** 17 Asian and 1 Caucasian	All patients had CSF neurochemistry diagnostic of AADC deficiency	Results for all 18 patients at 2 years post-gene therapy are currently available

[a] Patient disposition at the time of interim data analysis.

[b] Age at the time of eladocagene exuparvovec administration.

AADC, aromatic L-amino acid decarboxylase; CSF, cerebrospinal fluid; FDA, Food and Drug Administration

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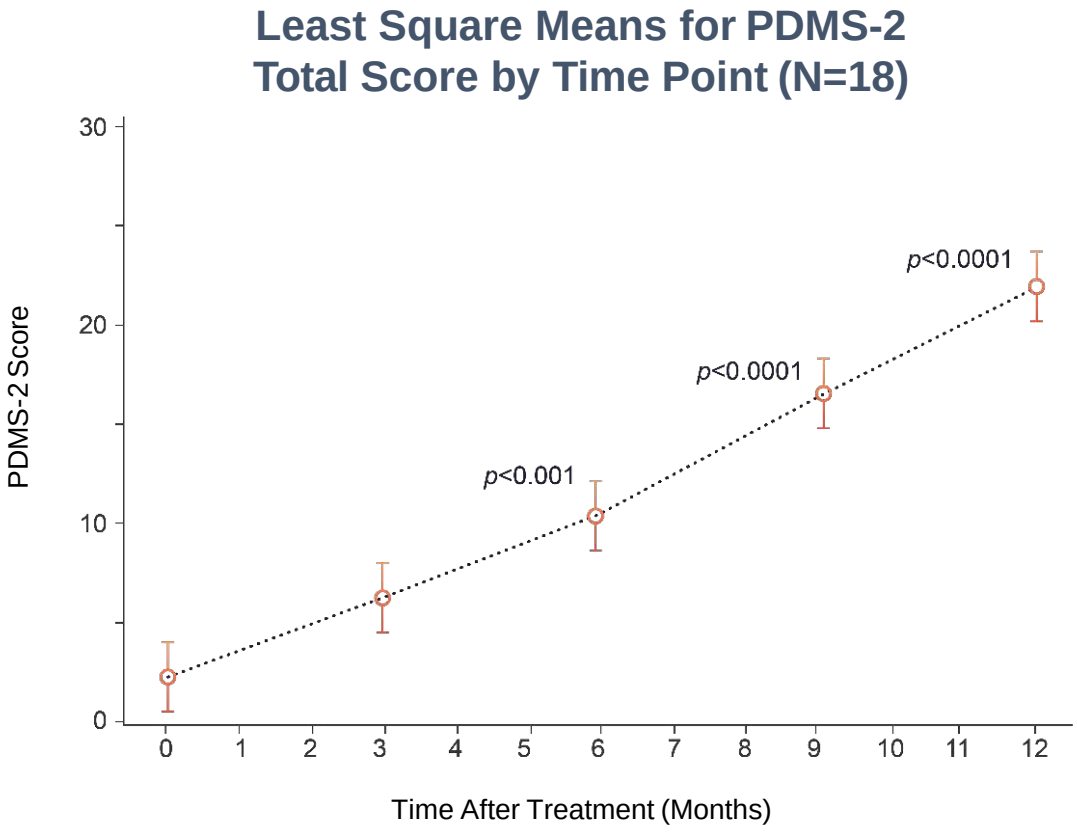
2. Wassenberg T, et al. *Orphanet J Rare Dis*. 2017;12(1):12. doi: 10.1186/s13023-016-0522-z.
3. Hwu WL, et al. *Sci Transl Med*. 2012;4(134):134ra161.

Motor function (change in PDMS-2 score) significantly improved over 12 months relative to natural history control in patients receiving eladocagene exuparvovec[1]



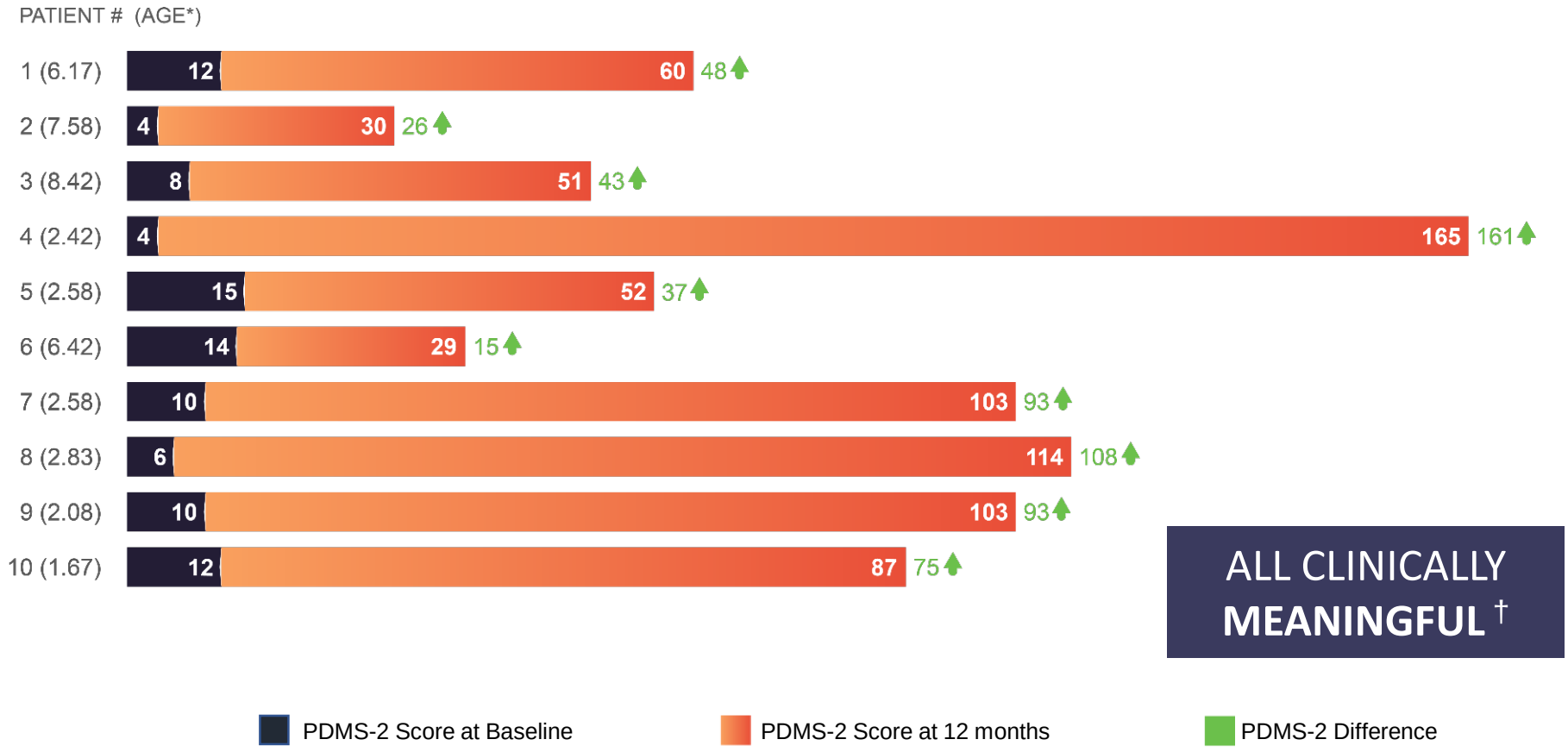
PDMS-2 Score

- In AADC-1601 and AADC-010, increases of more than 10 points on the PDMS-2 are clinically meaningful
- In AADC-1601 and AADC-010, mean increases in the PDMS-2 total score were statistically significant at 6, 9, and 12 months

PDMS-2, Peabody Developmental Motor Scale, version 2.

1. Chien YH, et al. Poster presented at: The 6th International Symposium on Paediatric Movement Disorders, February 7-8, 2019; Barcelona, Spain.

Individual PDMS-2 scores changes over 12 months showed clinically meaningful improvements in motor function in eladocagene exuparvovec trials[1]

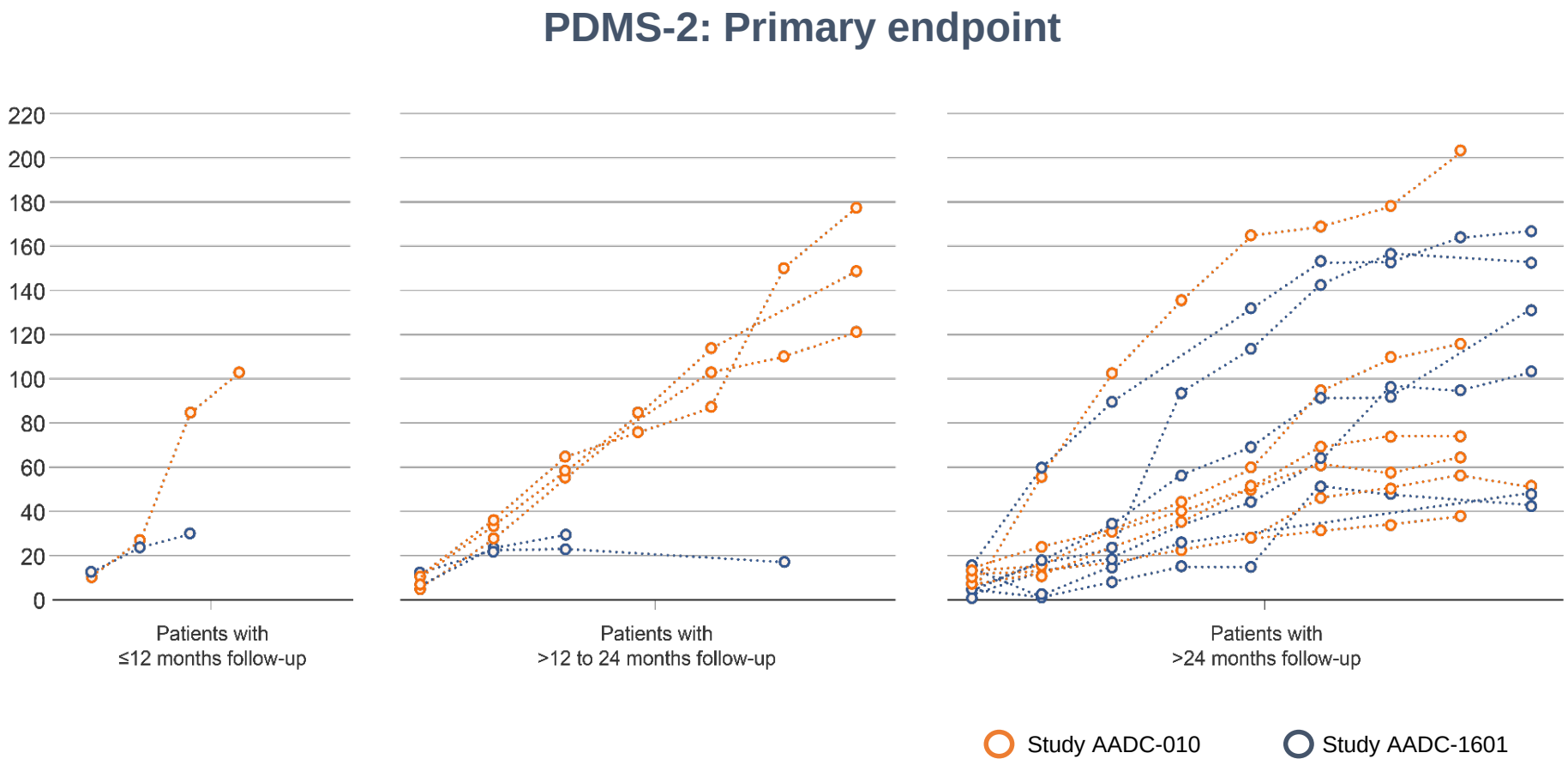


*Age at time of treatment initiation.

†Clinically meaningful changes as defined in the study: PDMS-2 scores ≥10 points.

1. Data on File. 2019.

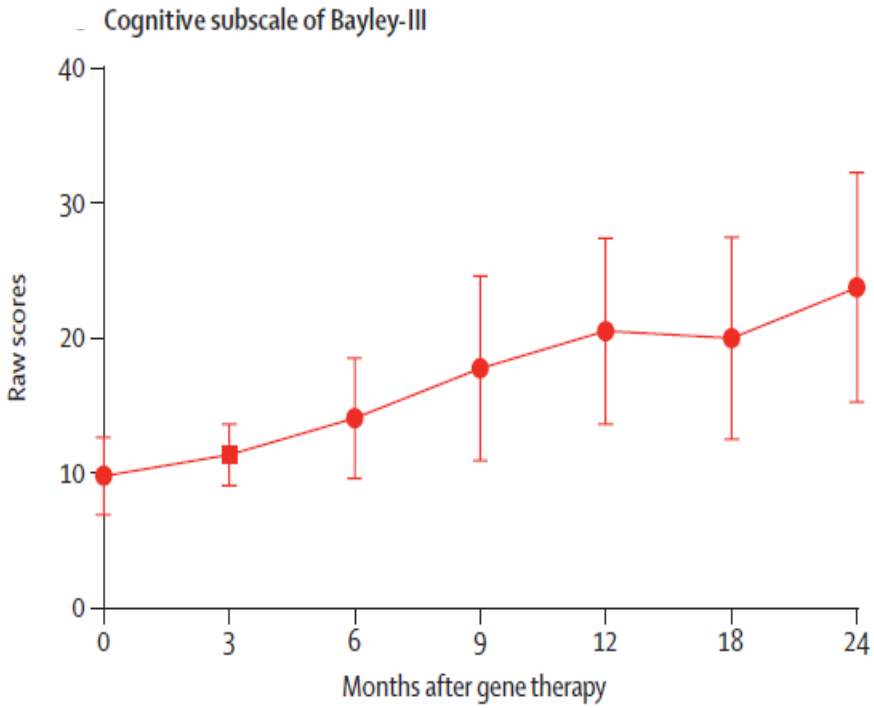
Clinical trials showed increases in individual motor function within 24 months of receiving eladocagene exuparvovec[1]



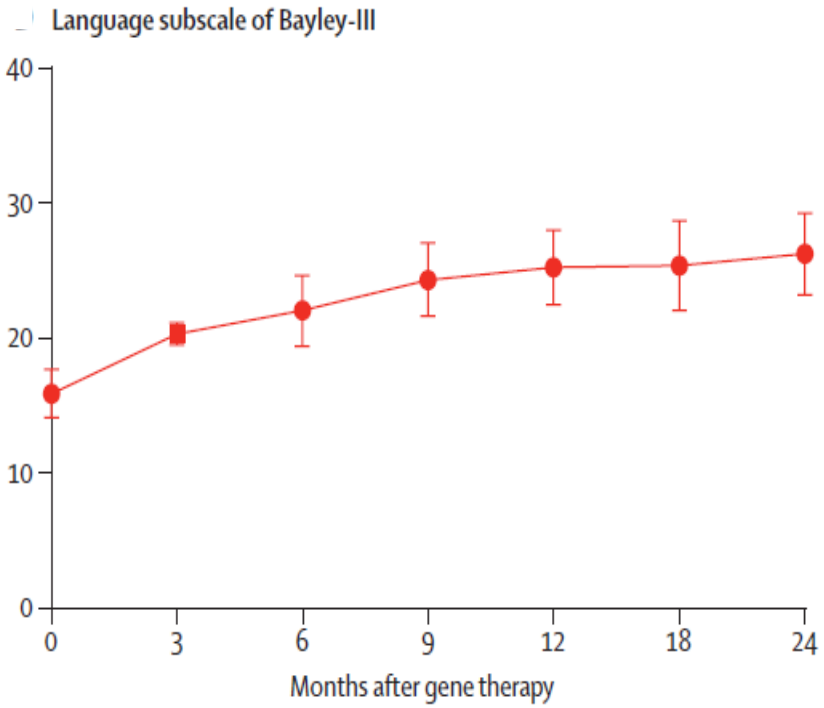
1. Data on File. 2019.

Improvements in cognitive function and language were observed through 24 months in patients receiving eladocagene exuparvovec: Bayley-III[1]

Cognition



Language



1. Data on File. 2018.

Significant proportion of patients achieve motor milestones after eladocagene exuparvovec administration compared with natural history[1]

- Two years after eladocagene exuparvovec, 8/18 gained full head control ($p<0.0001$), 6/18 could sit unassisted ($p<0.0001$), and 3 patients could stand with support ($p=0.005$)
- Beyond 2 years, amongst all 18 patients, half achieved a milestone
  - 7/18 (~40%) could sit unassisted
  - 5/18 (~30%) could stand with support

Number and Proportion of Patients Achieving **Key Motor Milestones** at 2 Years Post-treatment

Motor Milestone[a]	Time Point	Patients (N= 18)	Natural History Control Proportion (95% CI)	P-Value[b]
Head Control	Pre-Treatment	0 (0.0000)		
	Month 24	9 (0.5000)	0 (0.0000, 0.0440)	<0.0001
Sitting Unassisted	Pre-Treatment	0 (0.0000)		
	Month 24	7 (0.3889)	0 (0.0000, 0.0440)	<0.0001
Standing with Support	Pre-Treatment	0 (0.0000)		
	Month 24	2 (0.1111)	0 (0.0000, 0.0440)	0.1865
Walking with Assistance	Pre-Treatment	0 (0.0000)		
	Month 24	0 (0.0000)	0 (0.0000, 0.0440)	N/A

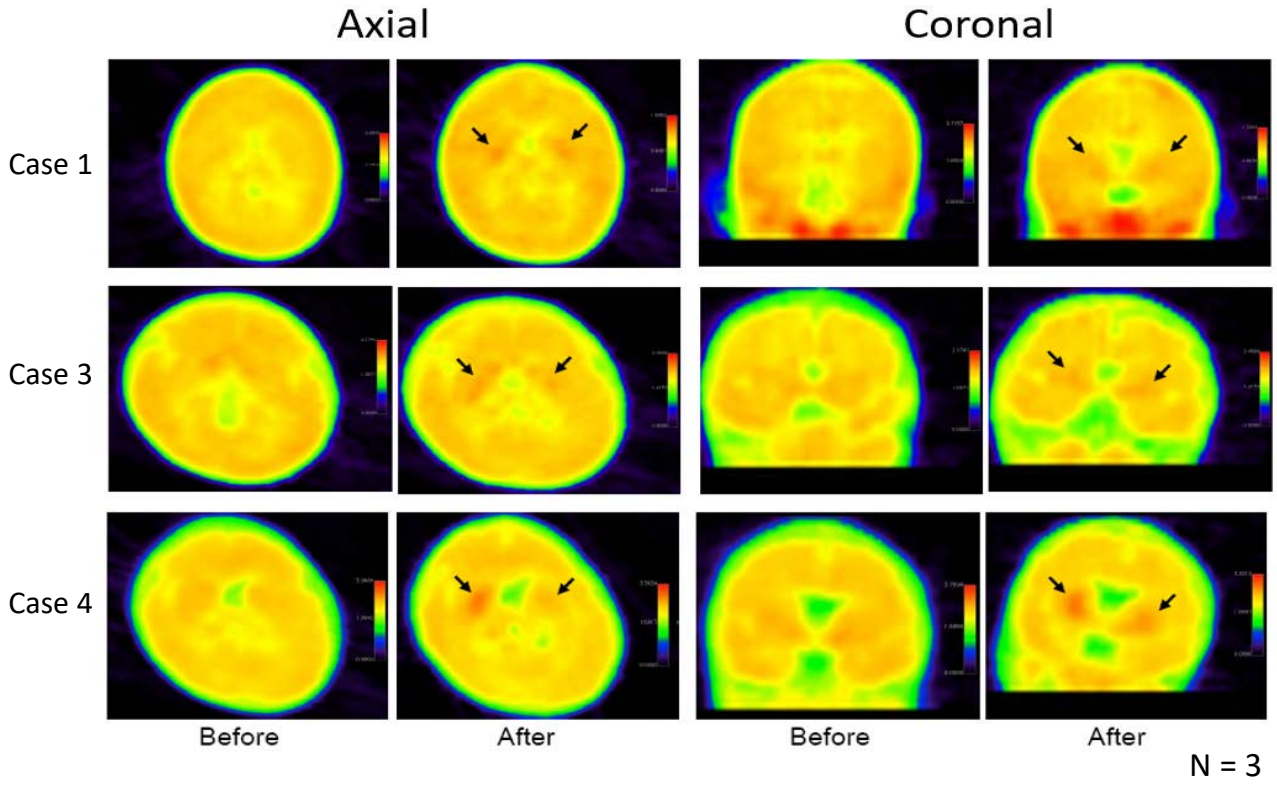
[a] Based on results of the PDMS-2.

[b] One-sided p-value for testing H0: proportion > historical control rate, for each milestone at the Month 24 time point.

1. Data on File. 2019.

Eladocagene exuparvovec increased AADC activity and resulted in *de novo* dopamine production over 12 months[1]

Visualized F-DOPA PET increases at baseline vs at 12 months after eladocagene exuparvovec administration



AADC, aromatic L-amino acid decarboxylase; F-DOPA PET, fluoro-3,4-dihydroxyphenylalnine positron emission tomography.

1. Hwu WL, et al. *Sci Transl Med*. 2012;4(134):134ra161.

Eladocagene exuparvovec appeared to be generally well tolerated in clinical trials[1]

Pooled Safety Results (N=18)	Common[a] AEs, n	Common[a] SAEs, n
Dyskinesia	17	0
Pyrexia	16	2
Diarrhea	12	0
Upper GI hemorrhage	6	0
Pneumonia	5	5
Cyanosis	5	2
Upper respiratory tract infection	5	0
Hypovolemic shock	0	2

- All dyskinesia events resolved over time, generally within 3 months and with no sequelae
- All SAEs were considered unrelated to eladocagene exuparvovec administration
- One SAE-related death was reported and attributed to post-influenza B encephalopathy

AE, adverse event; GI, gastrointestinal; SAE, serious adverse event.

[a] A common AE or SAE was defined as any AE or SAE occurring in >1 patient in either trial.

1. Data on File. 2018.

Safety and Efficacy Data

1 Intraputaminal administration of eladocagene exuparvovec in children with severe AADC deficiency: [1-3]

- Increased dopamine production with a significant increase in putamen F-DOPA PET specific uptake over first 12 months, secondary to increased AADC enzyme activity
- Significantly improved motor milestone acquisition from baseline after 12 months as measured by the PDMS-2 and provided clinically meaningful improvements out to 5 years
- Was generally well-tolerated
- Few serious adverse events, none considered related to treatment

2 Compared with a natural history cohort of patients with AADC deficiency,[4] a significant proportion of patients who received eladocagene exuparvovec gained motor milestones that they would not be expected to obtain over their lifetime

3 Gene therapy with eladocagene exuparvovec provides the potential for these patients to achieve and maintain motor milestones

AADC, aromatic L-amino acid decarboxylase.

1. Data on File. 2019.
2. Data on File. 2018.
3. Chien YH, et al. Poster presented at: the American Academy of Neurology (AAN) 2019 Annual Meeting; May 4-10, 2019; Philadelphia, PA.
4. Wassenberg T, et al. *Orphanet J Rare Dis*. 2017;12(1):12. doi: 10.1186/s13023-016-0522-z.

Summary of eladocagene exuparvovec to treat AADC deficiency

There are currently no FDA-approved therapies for AADC deficiency and current treatment options are limited and yield few improvements for the majority of patients

Eladocagene exuparvovec is a gene therapy consisting of an adeno-associated virus vector that delivers the human DDC gene to AADC-deficient cells in the CNS

Eladocagene exuparvovec is the first targeted gene therapy designed to restore AADC enzyme function and dopamine synthesis in the putamen to improve patients' motor function and development – as such, cannot be compared to any existing technology

Creating a unique ICD-10-PCS code will aid in accurately reporting and adjudicating claims for this treatment

Thank you