Eladocagene exuparvovec gene therapy improves motor development in patients with aromatic L-amino acid decarboxylase deficiency

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Introduction

- Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare genetic disorder caused by mutations in the dopa decarboxylase (*DDC*) gene encoding the AADC enzyme, resulting in marked dopamine loss that impedes normal motor development and the ability to attain key motor milestones, such as full head control, and the ability to sit, stand or walk.[1,2]
- Acquisition of early motor milestones are considered prerequisites to attain self-sufficient locomotion and motor function.
  - Without the attainment of these milestones, patients with AADC deficiency require life-long care.
- Eladocagene exuparvovec (PTC-AADC) is a gene therapy consisting of a recombinant adeno-associated viral vector serotype 2 containing the human cDNA encoding the AADC enzyme **(Figure 1)**.
- PTC-AADC was studied in patients with AADC deficiency in 2 clinical trials and 1 compassionate use trial.
  - Earlier data from these trials (AADC-CU/1601; AADC-010, NCT01395641; AADC-011, NCT02926066) demonstrated overall efficacy and safety of gene therapy with PTC-AADC in patients with AADC deficiency.[3]

Figure 1. PTC-AADC gene construct[4]

CMV IEP, human cytomegalovirus immediate-early promoter; ITR, adeno-associated virus serotype 2 inverted terminal repeat; HBG2/3, human beta globin partial intron 2/partial exon 3; Poly A, polyadenylation-containing sequence.

Objective

Here we present data from 3 trials on the efficacy of intraputaminal infusion of PTC-AADC on motor development in patients with AADC deficiency for ≤108 months after gene therapy (ranges from 3 months to 115 months) at 26 February 2020 cutoff.

Methods

- PTC-AADC was administered as a bilateral infusion in the putamen of 28 children with AADC deficiency in 3 single-centre trials (AADC-CU/1601 [compassionate use trial; 8 patients; completed], AADC-010 [phase 1/2 trial; 10 patients; completed] and AADC-011 [phase 2b trial; 10 patients to date; ongoing]).
- Patients were included in the trials if the following criteria were fulfilled:
  - Diagnosis of AADC deficiency indicated by characteristic cerebrospinal fluid (CSF) neurotransmitter metabolite profile and confirmed via enzyme activity test or genetic analysis of the *DDC* gene.
  - Exhibited classical clinical characteristics of AADC deficiency, including oculogyric crisis episodes, hypotonia and developmental retardation.
  - Age >2 years
  - Parents or guardians agreed to cooperate and signed informed consent.
- Patients received a total dose of 1.8×10^{11} vg (n=21) or 2.4×10^{11} vg (n=7; AADC-011, patients aged <3 years).
- Patients were assessed for the achievement of motor milestones using the Peabody Developmental Motor Scale, 2nd edition (PDMS-2) and the Alberta Infant Motor Scale (AIMS), 2 validated instruments used to study motor development in children.[5-7]
  - PDMS-2 contains subscales that measure interrelated motor abilities that develop early in life.[5]
    - Each item is scored on a scale from 0–2, with a score of 0 indicating the child cannot or will not attempt the item, a score of 1 indicating the child's performance shows a clear resemblance to the item mastery criteria but does not fully meet criteria, and a score of 2 meaning the child has mastered the item.
    - Specific motor skill items of the PDMS-2 were used to assess key motor milestones, shown in **Table 1** along with evaluation criteria.

Table 1. Evaluation criteria for achievement of key motor milestones

Motor milestone	Criteria required for score of: 2	1
Head control		
Partial-head control (Stationary Item #5)	Holds head in midline through 75%-100% of movement cycle	Holds head in midline through 50%-74% of movement cycle
Full-head control (Stationary Item #10)	Holds head aligned for 8 seconds while rotating head to follow toy	Holds head aligned for 4–7 sec while rotating head to follow toy
Sitting		
Sitting assisted (Stationary Item #11)	Maintains balance for 8 seconds	Maintains balance for 3-7 seconds
Sitting unassisted (Stationary Item #14)	Sits unsupported for 60 sec	Sits unsupported for 30–59 sec
Standing		
Standing with support (Locomotion Item #28)	Takes 4 alternative steps in place or forward	Takes 2–3 alternative steps in place or forward
Standing without support (Locomotion Item #31)	Maintains balance for 3 seconds before showing instability or dropping to floor	Maintains balance for 1-2 seconds before showing instability or dropping to floor
Walking		
Walking with assistance (Locomotion Item #34)	Uses alternating steps to walk 8 ft	Uses alternating steps to walk 4–7 ft
Walking without assistance (Locomotion Item #35)	Walk unaided for 5 steps	Walk unaided for 1-4 steps

  - AIMS contains 58 items divided into 4 subscales for elements of movement in different positions: prone, supine, sit and stand.[6,7]
    - Each item is scored as "observed" or "not observed," with 1 point given for each observed item.
- Motor milestones and development were measured every 3 months for the first year following gene therapy, then every 6–12 months for ≤108 months following PTC-AADC gene therapy.

Results

Patient demographics

- Baseline characteristics of full study populations are shown in **Table 2**.

Table 2. Baseline characteristics of study population

	AADC-CU/1601 (N=8)	AADC-010 (N=10)	AADC-011 (N=10)	Total (N=28)
Age at symptom onset, n (%)				
≤6 mo	2 (25.0)	9 (90.0)	7 (70.0)	18 (64.3)
≤12 mo	0 (0)	1 (10.0)	3 (30.0)	4 (14.3)
>12 mo	5 (62.5)	0 (0)	0 (0)	5 (17.9)
Unknown	1 (12.5)	0 (0)	0 (0)	1 (3.6)
Age at gene therapy, n (%)				
<2 y	0 (0)	1 (10.0)	4 (40.0)	5 (17.9)
2–<6 y	5 (62.5)	5 (50.0)	6 (60.0)	16 (57.1)
6–<12 y	3 (37.5)	4 (40.0)	0 (0)	7 (25.0)
Sex, n (%)				
Male	3 (37.5)	5 (50.0)	6 (60.0)	14 (50.0)
Female	5 (62.5)	5 (50.0)	4 (40.0)	14 (50.0)
Race, n (%)				
Asian-Chinese	0 (0)	9 (90.0)	7 (70.0)	16 (57.1)
White	0 (0)	1 (10.0)	0 (0)	1 (3.6)
Asian-Other	8 (100.0)	0 (0)	3 (30.0)	11 (39.3)

PDMS-2

- All patients treated with eladocagene exuparvovec showed clinically meaningful increases in total and subscale scores for PDMS-2 **(Table 3, Figure 2)**.
  - A clinically meaningful improvement for PDMS-2 is defined as an increase from baseline of 10 points.
- Increases from baseline in mean PDMS-2 total scores were seen as early as 3 months after treatment and positive changes from baseline in PDMS-2 total scores were observed through 108 months
- Overall attainment of motor milestones up to 108 months post-treatment (ranges from 3 months to 115 months) are listed in **Table 4**.

Table 3. LS means of CFB in PDMS-2 total and subscale scores (FAS population, N=28)

PDMS-2 subscale	Month 12 LS mean for CFB (SE)	Month 24 LS mean for CFB (SE)	Month 60 LS mean for CFB (SE)
Total score	66.9 (7.01)	95.4 (7.19)	115.0 (8.54)
Subscale			
Grasping	15.1 (1.66)	20.9 (1.72)	23.3 (2.13)
Locomotion	17.5 (2.57)	24.8 (2.63)	32.2 (3.15)
Object manipulation	0.3 (0.37)	1.3 (0.39)	2.3 (0.53)
Stationary	14.0 (1.40)	20.6 (1.44)	23.7 (1.72)
Visual-motor integration	20.4 (2.07)	28.5 (2.13)	34.1 (2.58)

CFB, change from baseline; FAS, full-analysis set; LS, least squares; PDMS-2, Peabody Developmental Motor Scale, 2nd Edition; SE, standard error.

Figure 2. PDMS-2 total scores by patient and chronological age through month 108 after gene therapy (N=28)

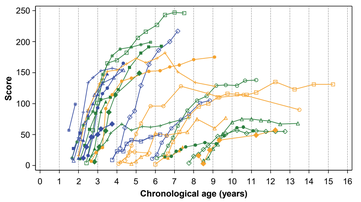


Table 4. Overall attainment of milestones up to month 108 post-gene therapy[a]

PDMS-2 milestones	Baseline	Up to M108
	Overall number of patients (N=28)	
Head control[b]	6	27
Sitting[c]	0	20
Standing[d]	0	9
Walking[e]	0	3

[a]Motor milestone achievement derived from the PDMS-2 results, and included scores of 1 and 2. [b]Head control included patients with partial or full head control [c]Sitting included patients who could sit assisted or unassisted [d]Standing included patients standing with or without support [e]Walking included patients walking with assistance or freely walking

AIMS

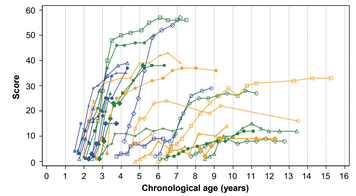
- Patients treated with eladocagene exuparvovec also demonstrated significant increases in total and subscale AIMS scores **(Table 5, Figure 3)**.
- These increases were similarly maintained or improved over time ≥60 months after gene therapy.

Table 5. LS means of CFB in AIMS total and subscale scores (FAS population, N=28)

AIMS subscale	Month 12 LS mean for CFB (SE)	Month 24 LS mean for CFB (SE)	Month 60 LS mean for CFB (SE)
Total score	16.6 (2.02)	24.2 (2.08)	27.5 (2.62)
Subscale			
Prone	6.4 (0.94)	9.1 (0.97)	10.4 (1.22)
Sit	3.6 (0.58)	6.9 (0.61)	7.3 (0.85)
Stand	1.0 (0.51)	2.1 (0.53)	3.3 (0.70)
Supine	5.9 (0.45)	6.4 (0.47)	6.9 (0.61)

AIMS, Alberta Infant Motor Scale; CFB, change from baseline; FAS, full-analysis set; LS, least squares; SE, standard error.

Figure 3. AIMS total scores by patient and chronological age through month 108 after gene therapy (N=28)



Safety

- Treatment-emergent adverse events (TEAEs) the treated population experienced are shown in **Table 6**, and the most common TEAEs (≥50% of patients) are shown in **Table 7**.
- Most AEs were mild or moderate in intensity; 11 patients had severe AEs.
- CSF leaks occurred in 3 patients; these events were considered related to the surgical procedure and not to the gene therapy and resolved without consequence.
- No viral shedding was detected in any patient through 12 months after gene therapy.

Table 6. TEAEs experienced across all 3 trials

	Overall (N=28)
Number of TEAEs	563
Patients with ≥1 TEAE, n (%)	28 (100)
TEAE definitely related to treatment, n (%)	0 (0)
Deaths[a], n (%)	2 (7.1)

TEAE, treatment-emergent adverse event.
[a]Deaths occurred 1 year and 5 years post-gene therapy and were considered unlikely to be related to treatment

Table 7. Summary of TEAEs (in ≥50% of patients)

Adverse event	1.8×10^{11} vg dose (N=21), n (%)	2.4×10^{11} vg dose (N=7), n (%)	Overall (N=28), n (%)
Pyrexia	20 (95.2)	7 (100.0)	27 (96.4)
Dyskinesia	21 (100.0)	3 (42.9)	24 (85.7)
Upper respiratory tract infection	14 (66.7)	6 (85.7)	20 (71.4)
Gastroenteritis	14 (66.7)	4 (57.1)	18 (64.3)
Pneumonia	16 (76.2)	2 (28.6)	18 (64.3)
Upper gastrointestinal haemorrhage	13 (61.9)	2 (28.6)	15 (53.6)

TEAE, treatment-emergent adverse event.

Conclusions

The data presented here from 3 trials of eladocagene exuparvovec in patients with AADC deficiency suggest that this gene therapy provides durable and meaningful benefits with a favourable safety profile.

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Disclosures

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References

1. Himmelreich N, et al. *Mol Genet Metab.* 2019;137(1):12-22.
2. Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12:12.
3. Chien YH, et al. *Lancet Child Adolesc Health.* 2017;1:265-273.
4. Chien YH, et al. AGIL-AADC gene therapy results in sustained improvements in motor and developmental milestones over 5 years in children with AADC deficiency.Presented at: Child Neurology Society Annual Meeting; Oct 23-26, 2019; Charlotte, NC.
5. Folio MR, et al. *Peabody Developmental Motor Scales: Examiner's Manual.* 2nd ed. Pro-Ed; 2000.
6. Darrah J, et al. *Dev Med Child Neurol.* 1998;40(7):485-491.
7. Piper MC, et al. *Can J Public Health.* 1992;83(suppl 2):S46-S50.

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