Gene therapy with eladocagene exuparvovec improves cognition and language in patients with aromatic L-amino acid decarboxylase deficiency

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Introduction

- Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive disorder caused by mutations in the dopa decarboxylase (*DDC*) gene encoding the AADC enzyme, resulting in marked dopamine loss that impedes normal motor development[1,2]
- Patients with AADC deficiency may experience delayed cognitive and speech development[2]
- Eladocagene exuparvovec (PTC-AADC) is a gene therapy consisting of a recombinant adeno-associated viral vector serotype 2 containing the human complementary DNA (cDNA) encoding the AADC enzyme **(Figure 1)**[3]
- 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.

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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 (OGC) episodes, hypotonia and developmental retardation
  - Greater than 2 years of age
  - Parents or guardians agreed to cooperate and signed informed consent
- Patients received a total dose of $1.8x10^{11}$ vg (n=21) or $2.4x10^{11}$ vg (n=7; AADC-011, patients <3 years of age)
- Cognition and language changes were assessed using the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT; AADC-CU/1601, n=8) and the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley-III; AADC-010 and AADC-011, n=20)
  - The CDIIT is used to evaluate the development of infants and toddlers and includes cognitive and language (comprehension and expression) subscales[5]
    - For each skill evaluated, the patient was given a score of 1 (passed) or 0 (not passed)
  - The Bayley-III is a standardized assessment of cognition, language and motor development for children between 1 and 42 months of age and includes cognitive and language subscales[6]
    - For each item, the patient was given a 1 (has the skill) or a 0 (does not have the skill)
- Cognition and language abilities were assessed every 3 months for the first year after gene therapy and every 6 months thereafter

Results

Patient demographics

- Baseline characteristics of full study populations are shown in **Table 1**

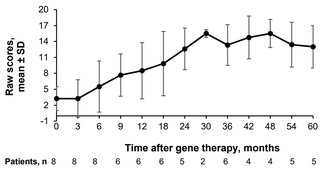
Table 1. Baseline characteristics of study population

	AADC-CU/1601 (N=8)	AADC-010 (N=10)	AADC-011 (N=10)	Overall (N=28)
Age at symptom onset n, (%)				
≤6 months	2 (25.0)	9 (90.0)	7 (70.0)	18 (64.3)
≤12 months	0 (0)	1 (10.0)	3 (30.0)	4 (14.3)
>12 months	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 years	0 (0)	1 (10.0)	4 (40.0)	5 (17.9)
2 to <6 years	5 (62.5)	5 (50.0)	6 (60.0)	16 (57.1)
6 to <12 years	3 (37.5)	4 (40.0)	0 (0)	7 (25.0)
Gender 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)

Measures of cognitive development

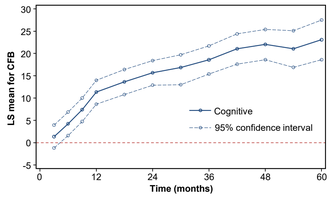
- CDIIT cognitive scores improved following PTC-AADC gene therapy **(Figure 2)**

Figure 2. Summary data for CDIIT cognitive scores following gene therapy (AADC-CU/1601)



- Total cognitive scores on the Bayley-III also improved following PTC-AADC gene therapy, with scores increasing as early as 3 months
- Changes from baseline through month 60 show an overall statistically significant improvement from baseline in Bayley-III total cognitive scores, with all lower bounds of 95% CI above 0 starting from month 6 (p<0.0001; **Figure 3**)

Figure 3. LS mean and 95% CI for change from baseline for Bayley-III cognitive scores following gene therapy (AADC-010 and AADC-011)

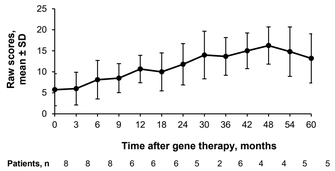


- Newly developed cognitive skills included reacting to the disappearance of a caregiver's face, persistently reaching for objects, responding to their image in a mirror, tracking yarn when moved vertically and looking for a fallen toy on the floor

Measures of language development

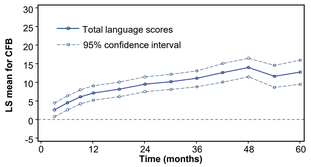
- CDIIT language scores showed gradual and sustained increases after gene therapy **(Figure 4),** indicating an improvement in communication following the therapy

Figure 4. Summary data for CDIIT language scores following gene therapy (AADC-CU/1601)



- Total language scores on the Bayley-III also showed gradual and sustained increases after gene therapy
- Changes from baseline through month 60 show statistically significant increases from baseline in Bayley-III total language and language subscale scores, with all lower bounds of 95% CI above 0 as early as month 3 (p<0.0001; **Figure 5**)

Figure 5. LS mean and 95% CI for change from baseline for Bayley-III total language score by visit (AADC-010 and AADC-011)



- Newly developed receptive language skills included turning their head toward sound, responding in an appropriate manner to at least 1 request and reacting when his or her name was called
- Newly developed expressive language skills included using 2-vowel sounds, 2 consonant sounds, imitating at least 1 consonant-vowel combination, jabbering and using 1-word approximations

Safety

- Treatment-emergent adverse events (TEAEs) experienced in the treated population are shown in **Table 2**, and the most common TEAEs (≥50% of patients) are shown in **Table 3**
- Most adverse events (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 2. TEAEs experienced across all 3 trials

	Overall (N=28)
Number of TEAEs	563
Patients with ≥1 TEAE, n (%)	28 (100.0)
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 3. Summary of TEAEs (in ≥50% of patients)

Adverse event	$1.8x10^{11}$ vg dose (N=21), n (%)	$2.4x10^{11}$ 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.

Objective

Here we present data from 3 trials on the efficacy of intraputaminal infusion of PTC-AADC on cognition and language in patients with AADC deficiency for up to 60 months post therapy (at 26 February 2020, cutoff date)

Conclusions

The results presented here demonstrate the efficacy of eladocagene exuparvovec in improving cognition and communication in patients with AADC deficiency, indicating that gene therapy may successfully target neurotransmitters affected by AADC deficiency and may improve quality of life. Such improvement in cognitive function in similar cohorts of patients with AADC deficiency has not been described.[1,2]

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Disclosures

Chun-Hwei Tai and Sheng-Hong Tseng have nothing to disclose. Panayiota Trifillis and Antonia Wang are employees of PTC Therapeutics, Inc. Tuna Koca is an employee of PTC Therapeutics Switzerland GmbH. Ni-Chung Lee has consulted for PTC Therapeutics, Inc. Yin-Hsiu Chien has served as an advisory board member for Asklepios BioPharmaceutical, Amicus Therapeutics, Biogen, Novartis, Sanofi and Takeda. He is or was a research investigator for Biogen and Sanofi, and is or was a consultant for Abeona Therapeutics, Biogen, Novartis and PTC Therapeutics, Inc. He has also served as a speaker for AveXis, Biogen, BioMarin, Novartis, Sanofi and Takeda. Paul Wuh-Liang Hwu has served as an advisory board member for, consulted for, and received research grants from PTC Therapeutics, Inc. He has also spoken at an event sponsored by PTC Therapeutics, Inc.

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