Eladocagene exuparvovec improves body weight and reduces respiratory infections in patients with aromatic L-amino acid decarboxylase deficiency

Paul Wuh-Liang Hwu,[1] Yin-Hsiu Chien,[1] Ni-Chung Lee,[1] Sheng-Hong Tseng,[1] Antonia Wang,[2] Panayiota Trifillis,[2] Tuna Koca,[3] Chun-Hwei Tai[1]

[1]National Taiwan University Hospital, Taipei, Taiwan; [2]PTC Therapeutics, Inc., South Plainfield, NJ; [3]PTC Therapeutics Switzerland GmbH., Zug, Switzerland

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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 typically exhibit feeding, swallowing and gastrointestinal problems throughout life, which may contribute to low body weight and a failure to thrive.[2]
- Additionally, respiratory infections and pneumonia are primary causes of morbidity in patients with AADC deficiency.[3]
- 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.[4]

Figure 1. PTC-AADC gene construct[5]

CMV IEP, human cytomegalovirus immediate-early promoter; ITR, adeno-associated virus serotype 2 inverted terminal repeat; hAADC, human *DDC* cDNA; 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 body weight and rate of respiratory infections and pneumonia in patients with AADC deficiency at 12 months and up to 5 years after therapy, respectively (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)
- Body weight at baseline and at a 12-month follow-up were compared with age- and gender-matched values for Taiwanese children without AADC deficiency.
- The number of patients experiencing respiratory infections and pneumonia, as well as the number of episodes and annual rate of respiratory infections and pneumonia, was measured annually for 5 years following PTC-AADC gene therapy.

Results

Patient demographics

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

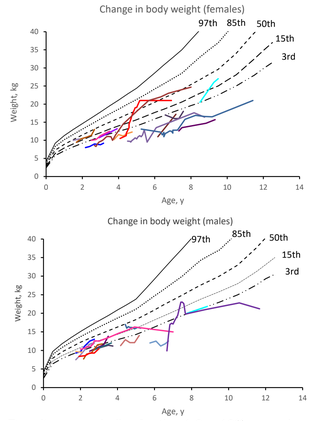
Table 1. Baseline characteristics of study population

	AADC-CU/1601 (N=8)	AADC-010 (N=10)	AADC-011 (N=10)	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)
Baseline height, cm				
Mean (SD)	96.00 (8.35)	98.60 (17.99)	84.69 (9.63)	92.89 (14.03)
Baseline weight, kg				
Mean (SD)	11.49 (2.67)	12.65 (4.67)	9.64 (1.41)	11.24 (3.39)
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)

Body weight

- At baseline, most patients (83.3%, 20/24) had a body weight ≤3rd percentile
- 12 months after gene therapy, 95.9% (23/24) of patients maintained or gained weight relative to age- and gender-matched children without AADC deficiency **(Figure 2)**.
  - 41.7% (10/24) shifted to a higher percentile.
  - 54.2% (13/24) maintained the same percentile as at baseline.
  - 4.2% (1/24) dropped to a lower percentile

Figure 2. Change in body weight following PTC-AADC gene therapy

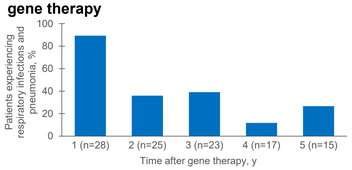


- Results were similar for the 1.8×10^{11} vg and 2.4×10^{11} vg groups.

Respiratory infections and pneumonia

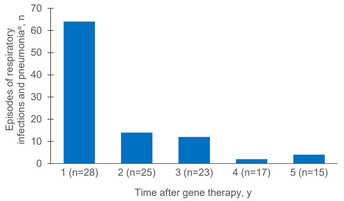
- The percentage of patients who experienced respiratory infections and pneumonia decreased following PTC-AADC gene therapy and was sustained up to 5 years after therapy **(Figure 3)**.

Figure 3. Percentage of patients experiencing respiratory infections and pneumonia following gene therapy



- The annual number of episodes of respiratory infections and pneumonia also showed a sustained decrease following PTC-AADC gene therapy as far as 5 years after treatment **(Figure 4)**.

Figure 4. Number of episodes of respiratory infections and pneumonia in patients 1–5 years after PTC-AADC gene therapy



[a]Combined annual rates of respiratory infections included rates of the following AE preferred terms: bronchiolitis, bronchitis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia mycoplasma, pneumonia viral, respiratory tract infection, stenotrophomonas infection, upper respiratory tract infection

- The annual rate of respiratory infections and pneumonia decreased for patients who received PTC-AADC gene therapy **(Table 2)**.

Table 2. Annual rate of respiratory infections and pneumonia after PTC-AADC gene therapy for patients who did not gain head control

	Time after gene therapy, y				
	1	2	3	4	5
Total # of patients	28	25	23	17	15
# of patients with AEs	25	9	9	2	4
% of patients with AEs	89.29	36.00	39.13	11.76	26.67
# of episodes	64	14	12	2	4
Annual rate	2.41	0.58	0.61	0.12	0.31

AE, adverse event.

Safety

- Treatment-emergent AEs (TEAEs) experienced in the treated population are shown in **Table 3**, and the most common TEAEs (≥50% of patients) are shown in **Table 4**.
- 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 3. 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 4. Summary of TEAEs (in ≥50% of patients)

AE	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

These results demonstrate the efficacy of eladocagene exuparvovec in increasing body weight and reducing respiratory infections in patients with AADC deficiency, changes that do not occur spontaneously in this patient population. Increase in body weight is a positive indicator for patients with AADC deficiency, who typically have low body weight.

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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, Biogen, Novartis, Sanofi and Takeda. He is or was a research investigator for Biogen and Sanofi, and is or was a consultant for Abeona, 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, 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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