

**Clinical trial results:****A Phase 1/2 Clinical Trial for Treatment of Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC (Eladocagene Exuparvovec)****Summary**

EudraCT number	2019-003032-23
Trial protocol	Outside EU/EEA
Global end of trial date	18 December 2020

**Results information**

Result version number	v1 (current)
This version publication date	31 August 2022
First version publication date	31 August 2022

**Trial information****Trial identification**

Sponsor protocol code	AADC-010
-----------------------	----------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01395641
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	National Taiwan University
Sponsor organisation address	7 Chung Shan South Road, Taipei City, Taiwan, 10002
Public contact	Wuh-Liang Hwu, National Taiwan University, 886 223123456 71938,
Scientific contact	Wuh-Liang Hwu, National Taiwan University, 886 223123456 71938,

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002435-PIP01-18
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2020
Global end of trial reached?	Yes
Global end of trial date	18 December 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objectives of this trial were to understand if the expression of human aromatic L-amino acid decarboxylase (hAADC) gene transferred by adeno-associated viral vector, serotype 2 (AAV2) vector may facilitate the conversion from L3,4-dihydroxyphenylalanine (L-DOPA) to dopamine to improve the motor function of participants; and to ensure the safety of hAADC gene transfer by AAV2 vector for children with AADC deficiency.

Protection of trial subjects:

This study was conducted in full accordance with the International Council for Harmonisation (ICH), Good Clinical Practice (GCP), Consolidated Guideline (E6), and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Taiwan: 10
Worldwide total number of subjects	10
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	9
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 10 participants were enrolled and treated in the study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Eladocagene Exuparvovec
------------------	-------------------------

Arm description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of  $0.45 \times 10^{11}$  viral genomes (vg) and a volume of 80 microliters ( $\mu\text{L}$ ) per site to 4 sites (2 per putamen), for a total dose of  $1.8 \times 10^{11}$  vg and a total volume of 320  $\mu\text{L}$ .

Arm type	Experimental
Investigational medicinal product name	Eladocagene Exuparvovec
Investigational medicinal product code	
Other name	AAV2-hAADC
Pharmaceutical forms	Solution for infusion
Routes of administration	Intracerebral use

Dosage and administration details:

Eladocagene exuparvovec gene therapy was administered in a single operative session using an established stereotactic neurosurgical procedure at a fixed dose.

<b>Number of subjects in period 1</b>	Eladocagene Exuparvovec
Started	10
Received gene therapy	10
Completed	9
Not completed	1
Death from Encephalitis due to Influenza B	1

## Baseline characteristics

### Reporting groups

Reporting group title	Eladocagene Exuparvovec
-----------------------	-------------------------

Reporting group description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of  $0.45 \times 10^{11}$  viral genomes (vg) and a volume of 80 microliters ( $\mu\text{L}$ ) per site to 4 sites (2 per putamen), for a total dose of  $1.8 \times 10^{11}$  vg and a total volume of 320  $\mu\text{L}$ .

Reporting group values	Eladocagene Exuparvovec	Total	
Number of subjects	10	10	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: months			
arithmetic mean	52.5		
standard deviation	$\pm 30.84$	-	
Gender Categorical Units: Subjects			
Female	5	5	
Male	5	5	
Neurotransmitter Metabolite Homovanillic Acid (HVA) Units: nanomoles (nmol)/liter (L)			
arithmetic mean	5.65		
standard deviation	$\pm 7.95$	-	
Neurotransmitter Metabolite 5-Hydroxyindoleacetic Acid (5-HIAA) Units: nmol/L			
arithmetic mean	3.10		
standard deviation	$\pm 1.29$	-	

## End points

### End points reporting groups

Reporting group title	Eladocagene Exuparvovec
-----------------------	-------------------------

Reporting group description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of  $0.45 \times 10^{11}$  viral genomes (vg) and a volume of 80 microliters ( $\mu\text{L}$ ) per site to 4 sites (2 per putamen), for a total dose of  $1.8 \times 10^{11}$  vg and a total volume of 320  $\mu\text{L}$ .

### Primary: Change From Baseline in Neurotransmitter Metabolite Homovanillic Acid (HVA) in Cerebrospinal Fluid at Month 12

End point title	Change From Baseline in Neurotransmitter Metabolite Homovanillic Acid (HVA) in Cerebrospinal Fluid at Month 12 <sup>[1]</sup>
-----------------	---

End point description:

The presence of neurotransmitter metabolite HVA (the metabolite of dopamine) was measured in cerebrospinal fluid (CSF). Intent-to-treat (ITT) population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this endpoint.

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: nmol/L				
arithmetic mean (standard deviation)	26.56 ( $\pm$ 21.57)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Neurotransmitter Metabolite 5-Hydroxyindoleacetic Acid (5-HIAA) in Cerebrospinal Fluid at Month 12

End point title	Change From Baseline in Neurotransmitter Metabolite 5-Hydroxyindoleacetic Acid (5-HIAA) in Cerebrospinal Fluid at Month 12 <sup>[2]</sup>
-----------------	---

End point description:

The presence of neurotransmitter metabolite 5-HIAA (the metabolite of serotonin) was measured in CSF. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Month 12

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this endpoint.

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: nmol/L				
arithmetic mean (standard deviation)	6.56 (± 12.72)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of Participants who Achieved an Increase of at least 10-Points From Baseline in Peabody Developmental Motor Scale, Second Edition (PDMS-2) Total Score at Month 12

End point title	Proportion of Participants who Achieved an Increase of at least 10-Points From Baseline in Peabody Developmental Motor Scale, Second Edition (PDMS-2) Total Score at Month 12 <sup>[3]</sup>
-----------------	--

End point description:

The PDMS-2 is a standardized, norm-referenced test, which includes gross motor and fine motor domains. All items of the PDMS-2 are scored on a 3-point scale (0 to 2): 0 is assigned when the child cannot perform the item or when the attempts do not meet the criteria of the item; 1 is assigned when the attempts do not meet for successful performance, but the behavior is emerging; and 2 indicates that the behavior is emerging, and the criterion for successful performance is fully met. The total score is the sum of all of the subscale scores (stationary, locomotion, object manipulation, grasping, visual-motor integration, and reflexes [the latter was not assessed in this population]) and varies based on age. The total score ranges from 0 to 482, where higher scores indicating more advanced motor function. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Primary
----------------	---------

End point timeframe:

Month 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this endpoint.

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: proportion of participants				
number (not applicable)	1.00			

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants who Achieved the Key Motor Milestones at Month 60

End point title	Percentage of Participants who Achieved the Key Motor Milestones at Month 60 <sup>[4]</sup>
-----------------	---

End point description:

PDMS-2 motor skill items assess key motor milestones of 1) full head control (Stationary Item 10), 2) sitting unassisted (Stationary Item 14), 3) standing with support (Locomotion Item 28), and 4) walking with assistance (Locomotion Item 34), as these were the key motor milestones used to define the natural history of participants with AAC deficiency. Each skill item was assessed as a 3-level scoring system: 0 = skill is not met, 1 = skill is emerging and shows a clear resemblance to mastery, and 2 = child has mastered the motor skill. For each of the 4 key motor milestones, the numeric score of "2" was translated into mastery of the milestone, indicating that the child achieved the milestone; a score of "1" translated into demonstrating emerging skill, and was often indicative of eventually mastering the milestone; a numeric score of "0," "or unscored" equated to "fail," and therefore the participant did not achieve the milestone. ITT population included all enrolled participants.

End point type	Primary
----------------	---------

End point timeframe:

Month 60

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this endpoint.

End point values	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)				
Full head control	70.0			
Sitting unassisted	60.0			
Standing with support	30.0			
Walking with assistance	20.0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Intracranial Bleeding That Required Surgical Treatment

End point title	Number of Participants With Intracranial Bleeding That Required Surgical Treatment
-----------------	--

End point description:

Safety analysis set included all treated participants

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to Month 60

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Craniotomy-induced Cerebrospinal Fluid (CSF) Exudation (CSF Leaks)

End point title	Number of Participants With Craniotomy-induced Cerebrospinal Fluid (CSF) Exudation (CSF Leaks)			
End point description:	Safety analysis set included all treated participants.			
End point type	Secondary			
End point timeframe:	Baseline up to Month 60			

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Adverse Events (AEs) Potentially Associated With Post-surgical Hyperactivity

End point title	Number of Participants With Adverse Events (AEs) Potentially Associated With Post-surgical Hyperactivity			
End point description:	AEs potentially associated with post-surgical hyperactivity included dyskinesia, diarrhoea, initial insomnia, and salivary hypersecretion. Safety analysis set included all treated participants			
End point type	Secondary			
End point timeframe:	Baseline up to Month 60			

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
Dyskinesia	10			
Diarrhoea	7			
Initial insomnia	4			
Salivary hypersecretion	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)
End point description:	An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs are those AEs with an onset on or after the surgery start time; AEs with a missing onset date were considered treatment emergent. AEs included both SAEs and non-serious AEs. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. Safety analysis set included all treated participants.
End point type	Secondary
End point timeframe:	Baseline up to Month 60

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants	10			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Body Weight at Month 12

End point title	Change From Baseline in Body Weight at Month 12
End point description:	ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.
End point type	Secondary
End point timeframe:	Baseline, Month 12

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: kilograms (kg)				
arithmetic mean (standard deviation)	3.39 (± 2.05)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Putaminal Positron Emission Tomography (PET)-Specific Uptake at Month 60

End point title	Change From Baseline in Putaminal Positron Emission Tomography (PET)-Specific Uptake at Month 60			
End point description:	<p>Expression and activity of the AADC enzyme in the putamen was assessed by PET imaging using L-6-[18F] fluoro-3,4-dihydroxyphenylalanine (18F-DOPA), a positron-emitting fluorine-labeled version of levodopa, which is a substrate for AADC. The 18F-DOPA is administered intravenously, crosses the blood-brain barrier, and is taken up by the presynaptic nigrostriatal dopaminergic neurons in the putamen and converted by AADC to dopamine. Therefore, increased 18F-DOPA putamen uptake over time objectively demonstrates newly produced dopamine and the presence of functional AADC enzyme. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.</p>			
End point type	Secondary			
End point timeframe:	Baseline, Month 60			

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: millicurie (mCi)				
arithmetic mean (standard deviation)	0.46 (± 0.17)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in PDMS-2 Total Score at Month 60

End point title	Change From Baseline in PDMS-2 Total Score at Month 60			
End point description:	<p>The PDMS-2 is a standardized, norm-referenced test, which includes gross motor and fine motor</p>			

domains. All items of the PDMS-2 are scored on a 3-point scale (0 to 2): 0 is assigned when the child cannot perform the item or when the attempts do not meet the criteria of the item; 1 is assigned when the attempts do not meet for successful performance, but the behavior is emerging; and 2 indicates that the behavior is emerging, and the criterion for successful performance is fully met. The total score is the sum of all of the subscale scores (stationary, locomotion, object manipulation, grasping, visual-motor integration, and reflexes [the latter was not assessed in this population]) and varies based on age. The total score ranges from 0 to 482, where higher scores indicating more advanced motor function. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Month 60	

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units on a scale				
arithmetic mean (standard deviation)	122.13 ( $\pm$ 77.21)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Bayley Scale of Infant and Toddler Development, Third Edition [Bayley-III] Total Score at Month 60

End point title	Change From Baseline in Bayley Scale of Infant and Toddler Development, Third Edition [Bayley-III] Total Score at Month 60
-----------------	--

End point description:

The Bayley-III has 5 main subscales: Cognitive Scale, Language Scale (expressive and receptive), Motor Scale, Social Emotional Scale, and Adaptive Behavior Scale. The Cognitive Scale includes items such as attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play. The Language Scale includes understanding and expression of language, for example, recognition of objects and people, following directions, and naming objects and pictures. The study only used the cognitive scales and language scales for evaluation, and Bayley-III "total" score (refers to the sum of the Cognition, Expressive Communication, and Receptive Communication subscales) ranges from 40 to 160, where higher score indicated stronger skills and abilities and lower scores indicate possible delay/deficit. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Month 60	

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units on a scale				
arithmetic mean (standard deviation)	39.75 (± 20.01)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Alberta Infant Motor Scale (AIMS) Total Score at Month 60

End point title	Change From Baseline in Alberta Infant Motor Scale (AIMS) Total Score at Month 60
-----------------	--

End point description:

The AIMS is a validated, 58-item observational measure that assesses the sequential development of motor milestones. Each item is scored as "observed" or "not observed," and a point is given for each observed item. The AIMS total score is calculated by summing the scores for the 58 items, with a range of scores from 0 to 58. Higher scores indicate more advanced motor function. Each of the 58 items consists of an artist's drawing and a photograph of a young child performing a particular movement. The AIMS scale requires minimal handling of the child and assesses the child's movement in 4 positions: prone, supine, sitting, and standing. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Month 60

<b>End point values</b>	Eladocagene Exuparvovec			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units on a scale				
arithmetic mean (standard deviation)	25.88 (± 18.65)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Month 60

Adverse event reporting additional description:

Safety analysis set included all treated participants.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

### Reporting groups

Reporting group title	Eladocagene Exuparvovec
-----------------------	-------------------------

Reporting group description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of  $0.45 \times 10^{11}$  viral genomes (vg) and a volume of 80 microliters ( $\mu\text{L}$ ) per site to 4 sites (2 per putamen), for a total dose of  $1.8 \times 10^{11}$  vg and a total volume of 320  $\mu\text{L}$ .

Serious adverse events	Eladocagene Exuparvovec		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Developmental hip dysplasia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Polydactyly			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis influenzal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia influenzal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	5 / 10 (50.00%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Post procedural pneumonia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Eladocagene Exuparvovec		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vascular disorders			
Cyanosis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	4		
Pallor			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	10 / 10 (100.00%) 15		
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Oedema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Reproductive system and breast disorders Genital erythema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3		
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hypoxia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5		
Investigations			

Breath sounds abnormal subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Oxygen saturation decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injury, poisoning and procedural complications Thermal burn subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Tooth fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Congenital, familial and genetic disorders Developmental hip dysplasia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Testotoxicosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Nervous system disorders Cerebrospinal fluid leakage subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Seizure subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Loss of consciousness			

<p>subjects affected / exposed occurrences (all)</p> <p>Vocal cord paralysis subjects affected / exposed occurrences (all)</p> <p>Dyskinesia subjects affected / exposed occurrences (all)</p>	<p>1 / 10 (10.00%) 1</p> <p>1 / 10 (10.00%) 2</p> <p>10 / 10 (100.00%) 18</p>		
<p>Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)</p>	<p>1 / 10 (10.00%) 1</p>		
<p>Ear and labyrinth disorders Allergic otitis media subjects affected / exposed occurrences (all)</p>	<p>1 / 10 (10.00%) 1</p>		
<p>Eye disorders Eyelid disorder subjects affected / exposed occurrences (all)</p> <p>Astigmatism subjects affected / exposed occurrences (all)</p> <p>Ocular hyperaemia subjects affected / exposed occurrences (all)</p>	<p>1 / 10 (10.00%) 1</p> <p>1 / 10 (10.00%) 1</p> <p>1 / 10 (10.00%) 1</p>		
<p>Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all)</p> <p>Diarrhoea subjects affected / exposed occurrences (all)</p> <p>Enteritis subjects affected / exposed occurrences (all)</p> <p>Gastrooesophageal reflux disease</p>	<p>2 / 10 (20.00%) 2</p> <p>5 / 10 (50.00%) 9</p> <p>1 / 10 (10.00%) 1</p>		

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Mouth ulceration subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Oral mucosa erosion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Salivary hypersecretion subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Stress ulcer subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Upper gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 7		
Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders			
Decubitus ulcer subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Dermatitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Eczema subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Endocrine disorders Precocious puberty			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders			
Lordosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Scoliosis			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Bronchiolitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Acute sinusitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	4		
Gingivitis			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
Pneumonia influenzal			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Otitis media acute subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 12		
Viral rash subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
<b>Metabolism and nutrition disorders</b>			
Dehydration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Feeding disorder subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2014	<ul style="list-style-type: none"><li>• Updated background information for AADC deficiency in Taiwan;</li><li>• Updated treatment information for AADC deficiency with citation of recent articles;</li><li>• Expanded the description of the mechanism of action of PD;</li><li>• Added preclinical study results;</li><li>• Added description of infusion of AADC vector;</li><li>• Specified the number of post-study visits and associated procedures;</li><li>• Removed details of by-visit procedures as they are present in the summary of items and schedules of treatment and examinations;</li><li>• Added a subsection describing dosage and infusion of viral vector;</li><li>• Added a subsection on allowable concomitant medications;</li><li>• Added a new section describing the expected duration of the study;</li><li>• Added a new section header for classifying the radiologic and functional assessments to be used for postsurgical evaluation;</li><li>• Added subsection on treatment and examination procedures to be performed at each stage of the study;</li><li>• New section added to provide timing of standardized rehabilitation therapy;</li><li>• Modified the endpoints to evaluate neurotransmitter metabolites and assess PDMS-2 score;</li><li>• Modified the secondary endpoints to add evaluation of craniotomy-induced CSF exudation and effect on feeding and need for nasogastric tube as well as adding collection of severity information for adverse events;</li><li>• New section added to describe the preparation of AAV2-hAADC viral vector and genome titers;</li><li>• Included a summary of AAV2-hAADC toxicity in rats;</li><li>• New section added to hypothesize the anticipated outcomes of the study;</li><li>• New section header added along with introductory paragraph describing the collection of information on AEs, TEAEs, and SAEs;</li><li>• Added description for management of severe symptoms;</li><li>• Added description on risks of study evaluation, including respiratory risk, use of anesthesia, and lumbar puncture;</li><li>• Added statements summarizing the damage and insurance compensation and withdrawal from the study;</li></ul>
23 May 2019	Updated information on subinvestigators.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported