Clinical trial results:
A Clinical Trial for Treatment of Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC - An Expansion

Summary

EudraCT number	2019-003072-39
Trial protocol	Outside EU/EEA
Global end of trial date	24 January 2022

Results information

Result version number	v1 (current)
This version publication date	01 September 2022
First version publication date	01 September 2022

Trial information

Trial identification

Sponsor protocol code	NTUH-AADC-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02926066
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Taiwan University Hospital
Sponsor organisation address	7 Chung Shan South Road, Taipei City, Taiwan, 10002
Public contact	Yin-Hsiu Chien, National Taiwan University Hospital, Department of Pediatrics and Medical Genetics, 886 2 23123456 71937,
Scientific contact	Yin-Hsiu Chien, National Taiwan University Hospital, Department of Pediatrics and Medical Genetics, 886 2 23123456 71937,

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	19 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2022
Global end of trial reached?	Yes
Global end of trial date	24 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the safety and efficacy of eladocagene exuparvovec in AADC-deficient participants who were not enrolled into the Phase 1/2 trial (AADC-010). This study was designed to extend the experience in this gene therapy and to slightly increase the dosage in participants younger than 3 years old.

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	09 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Ethical reason, Scientific research, Safety
Long term follow-up duration	13 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Taiwan: 12
Worldwide total number of subjects	12
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)	6
Children (2-11 years)	6
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:

Individuals with a confirmed diagnosis of AADC deficiency between the ages of 2 and 6 at time of surgery were eligible to participate in the study.

Pre-assignment

Screening details:

A total of 12 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

Are arms mutually exclusive?	Yes
Arm title	Eladocagene Exuparvovec 1.8×10^11 vg

Arm description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.45×10^11 viral genomes (vg) and a volume of 80 microliters (µL) per site to 4 sites (2 per putamen), for a total dose of 1.8×10^11 vg and a total volume of 320 µL.

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.

Arm title	Eladocagene Exuparvovec 2.4×10^11 vg

Arm description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.6×10^11 vg and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of 2.4×10^11 vg and a total volume of 320 µL.

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.

Number of subjects in period 1	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg
Started	3	9
Completed	3	9

Baseline characteristics

Reporting groups

Reporting group title	Eladocagene Exuparvovec 1.8×10^11 vg
Reporting group description:	
Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.45×10^11 viral genomes (vg) and a volume of 80 microliters (µL) per site to 4 sites (2 per putamen), for a total dose of 1.8×10^11 vg and a total volume of 320 µL.	
Reporting group title	Eladocagene Exuparvovec 2.4×10^11 vg
Reporting group description:	
Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.6×10^11 vg and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of 2.4×10^11 vg and a total volume of 320 µL.	

Reporting group values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Total
Number of subjects	3	9	12
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	6	6
Children (2-11 years)	3	3	6
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	55.0	23.3	
standard deviation	± 13.23	± 3.32	-
Gender Categorical			
Units: Subjects			
Female	1	3	4
Male	2	6	8

Subject analysis sets

Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants treated with eladocagene exuparvovec.	

Reporting group values	Overall		
Number of subjects	12		

Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	6		
Children (2-11 years)	6		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean	31.3		
standard deviation	± 15.65		
Gender Categorical Units: Subjects			
Female	4		
Male	8		

End points

End points reporting groups

Reporting group title	Eladocagene Exuparvovec 1.8×10^11 vg

Reporting group description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.45×10^11 viral genomes (vg) and a volume of 80 microliters (µL) per site to 4 sites (2 per putamen), for a total dose of 1.8×10^11 vg and a total volume of 320 µL.

Reporting group title	Eladocagene Exuparvovec 2.4×10^11 vg

Reporting group description:

Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.6×10^11 vg and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of 2.4×10^11 vg and a total volume of 320 µL.

Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants treated with eladocagene exuparvovec.

Primary: Proportion of Participants Achieving Key Motor Milestones at Month 12, Assessed Using the Peabody Developmental Motor Scale, Second Edition (PDMS-2)

End point title	Proportion of Participants Achieving Key Motor Milestones at Month 12, Assessed Using the Peabody Developmental Motor Scale, Second Edition (PDMS-2)[1]

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 key motor milestones used to define the natural history of participants with AADC deficiency. Skill items were 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, numeric score of "2" was translated into mastery of the milestone, indicating that the child achieved the milestone; score of "1" translated into demonstrating emerging skill, and was often indicative of eventually mastering the milestone; score of "0," "or unscored" equated to "fail," and therefore the participant did not achieve the milestone. Intent-to-treat (ITT) population included all enrolled participants.

End point type	Primary

End point timeframe:

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: As per statistical analysis plan, no statistical analysis was conducted.

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[2]	10	
Units: proportion of participants				
number (confidence interval 95%)				
Achieved full head control (score of 2)	0.3333 (0.0084 to 0.9057)	0.8571 (0.4213 to 0.9964)	0.7000 (0.3475 to 0.9333)	
Achieved sitting unassisted (score of 2)	0.0000 (0.0000 to 0.7076)	0.4286 (0.0990 to 0.8159)	0.3000 (0.0667 to 0.6525)	

Achieved standing with support (score of 2)	0.0000 (0.0000 to 0.7076)	0.0000 (0.0000 to 0.4096)	0.0000 (0.0000 to 0.3085)	
Achieved walking with assistance (score of 2)	0.0000 (0.0000 to 0.7076)	0.0000 (0.0000 to 0.4096)	0.0000 (0.0000 to 0.3085)	

Notes:

[2] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

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[3]

End point description:

The presence of neurotransmitter metabolite HVA (the metabolite of dopamine) was measured in cerebrospinal fluid (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:

[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: As per statistical analysis plan, no statistical analysis was conducted.

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[4]	10	
Units: nmol/L				
arithmetic mean (standard deviation)				
Baseline	16.17 (± 17.58)	16.44 (± 16.16)	16.38 (± 15.69)	
Change from Baseline	15.17 (± 3.88)	25.07 (± 16.16)	22.10 (± 14.16)	

Notes:

[4] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Neurotransmitter Metabolite 5-Hydroxyindoleacetic Acid (5-HIAA) in Cerebrospinal Fluid (CSF) at Month 12[5]

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:

[5] - 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: As per statistical analysis plan, no statistical analysis was conducted.

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[6]	10	
Units: nmol/L				
arithmetic mean (standard deviation)				
Baseline	15.17 (± 10.98)	7.33 (± 6.03)	9.29 (± 7.81)	
Change from Baseline	-12.67 (± 10.98)	0.86 (± 8.54)	-3.20 (± 10.87)	

Notes:

[6] - Only 7 of the 9 enrolled participants were assessed at Month 12.

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 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 PDMS-2 Total Score at Month 12[7]

End point description:

The PDMS-2 is a validated instrument used to measure motor skills and developmental milestone achievement in infants and children. The PDMS-2 total score is calculated by summing the scores for the 249 items; each skill item was assessed as a simple, 3-level scoring system:
0 = the skill is not met,
1 = the skill is emerging and shows a clear resemblance to mastery of the skill item, and
2 = the child has mastered the motor skill.
PDMS2-Total score ranges from 0 to 498.
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:

[7] - 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: As per statistical analysis plan, no statistical analysis was conducted.

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[8]	10	
Units: proportion of participants				
number (not applicable)	1.00	1.00	1.00	

Notes:

[8] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PDMS-2 Total Score at Month 12

End point title	Change From Baseline in PDMS-2 Total Score at Month 12

End point description:

The PDMS-2 is a validated instrument used to measure motor skills and developmental milestone achievement in infants and children. The PDMS-2 total score is calculated by summing the scores for the 249 items; each skill item was assessed as a simple, 3-level scoring system:
0 = the skill is not met,
1 = the skill is emerging and shows a clear resemblance to mastery of the skill item, and
2 = the child has mastered the motor skill.
PDMS2-Total score ranges from 0 to 498.
An increase from baseline indicates 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 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[9]	10	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	14.67 (± 10.02)	19.00 (± 14.96)	17.92 (± 13.59)	
Change from Baseline	61.33 (± 37.07)	101.29 (± 29.15)	89.30 (± 35.28)	

Notes:

[9] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Alberta Infant Motor Scale (AIMS) Total Score at Month 12

End point title	Change From Baseline in Alberta Infant Motor Scale (AIMS) Total Score at Month 12

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 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[10]	10	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	4.00 (± 3.46)	2.56 (± 1.13)	2.92 (± 1.88)	
Change from Baseline	13.67 (± 12.50)	23.57 (± 6.27)	20.60 (± 9.16)	

Notes:

[10] - Only 7 of the 9 enrolled participants were assessed at Month 12.

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 12

End point title	Change From Baseline in Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III) Total Score at Month 12

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 a higher score indicated stronger skills and abilities and lower scores indicated 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 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[11]	10	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	35.00 (± 4.36)	34.56 (± 7.40)	34.67 (± 6.58)	
Change from Baseline	10.00 (± 5.57)	21.57 (± 3.36)	18.10 (± 6.76)	

Notes:

[11] - Only 7 of the 9 enrolled participants were assessed at Month 12.

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 13

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	9	12	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Craniotomy-induced 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 13

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	9	12	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Post-hoc: 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	Post-hoc

End point timeframe:

Baseline, Month 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[12]	10	
Units: kilograms (kg)				
arithmetic mean (standard deviation)				
Baseline	11.17 (± 0.91)	9.10 (± 1.04)	9.62 (± 1.34)	
Change from Baseline	1.77 (± 1.14)	2.51 (± 1.45)	2.29 (± 1.35)	

Notes:

[12] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change From Baseline in Putaminal Positron Emission Tomography (PET)-Specific Uptake at Month 12

End point title	Change From Baseline in Putaminal Positron Emission Tomography (PET)-Specific Uptake at Month 12

End point description:

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. An increase in 18F-DOPA putamen uptake over time demonstrates newly produced dopamine and the presence of functional AADC enzyme.

PET 18F-fluorodopa uptake values were used to compute the specific uptake at each time point as follows:
specific uptake = ((left putamen-occipital lobe) + (right putamen-occipital lobe))/2 occipital lobe
ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Post-hoc

End point timeframe:

Baseline, Month 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[13]	10	
Units: specific uptake value				
arithmetic mean (standard deviation)				
Baseline	0.52 (± 0.05)	0.26 (± 0.13)	0.32 (± 0.17)	
Change from Baseline	-0.03 (± 0.07)	0.43 (± 0.27)	0.29 (± 0.32)	

Notes:

[13] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Participants Achieving Additional Motor Milestones Assessed Using the PDMS-2

End point title	Percentage of Participants Achieving Additional Motor Milestones Assessed Using the PDMS-2

End point description:

Additional motor milestones of partial head control, sitting with assistance, and crawling were assessed using the PDMS-2. Each motor skill item was assessed as a 3-level scoring system: 0 = the skill is not met, 1 = the skill is emerging and shows a clear resemblance to mastery of the skill item, and 2 = the child has mastered the motor skill. For each additional motor milestones, numeric score of "2" was translated into mastery of the milestone, indicating that the child achieved the milestone; score of "1" translated into demonstrating emerging skill; score of "0," "or unscored" equated to "fail," and therefore the participant did not achieve the milestone. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Post-hoc

End point timeframe:

Month 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7[14]	10	
Units: percentage of participants				
number (not applicable)				

Achieved partial head control (score of 2)	33	71	60	
Achieved sitting with assistance (score of 2)	33	43	40	
Achieved crawling (score of 2)	0	0	0	

Notes:

[14] - Only 7 of the 9 enrolled participants were assessed at Month 12.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Fine Motor Grasping Total Scores Assessed Using the PDMS-2

End point title	Fine Motor Grasping Total Scores Assessed Using the PDMS-2

End point description:

Based on total scores of the PDMS-2 fine motor skills of grasping rattle sitting on lap, grabbing cube fingers space, grasping pellets, manipulating paper, grasping pellets thumb, and grasping pellets pad. Each skill item was assessed as a simple, 3-level scoring system: 0 = the skill is not met, 1 = the skill is emerging and shows a clear resemblance to mastery of the skill item, and 2 = the child has mastered the motor skill. The total score is determined by the sum of the points of each subscale/item. ITT population included all enrolled participants. Here, overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Post-hoc

End point timeframe:

Month 12

End point values	Eladocagene Exuparvovec 1.8×10^11 vg	Eladocagene Exuparvovec 2.4×10^11 vg	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	7	10	
Units: units on a scale				
arithmetic mean (standard deviation)	6.33 (± 6.028)	6.57 (± 3.735)	6.50 (± 4.170)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Month 13	
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 1.8×10^11 vg
Reporting group description:	
Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.45×10^11 viral genomes (vg) and a volume of 80 microliters (µL) per site to 4 sites (2 per putamen), for a total dose of 1.8×10^11 vg and a total volume of 320 µL.	
Reporting group title	Overall
Reporting group description:	
All participants treated with eladocagene exuparvovec.	
Reporting group title	Eladocagene Exuparvovec 2.4×10^11 vg
Reporting group description:	
Participants received eladocagene exuparvovec administered during a single operative session at a dose of 0.6×10^11 vg and a volume of 80 µL per site to 4 sites (2 per putamen), for a total dose of 2.4×10^11 vg and a total volume of 320 µL.	

Serious adverse events	Eladocagene Exuparvovec 1.8×10^11 vg	Overall	Eladocagene Exuparvovec 2.4×10^11 vg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	12 / 12 (100.00%)	9 / 9 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Paranasal sinus inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exanthema subitum			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 3 (66.67%)	4 / 12 (33.33%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Parainfluenzae virus infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 12 (25.00%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 3 (100.00%)	5 / 12 (41.67%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Eladocagene Exuparvovec 1.8×10^11 vg	Overall	Eladocagene Exuparvovec 2.4×10^11 vg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	12 / 12 (100.00%)	9 / 9 (100.00%)
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Cyanosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	7 / 12 (58.33%)	6 / 9 (66.67%)
occurrences (all)	1	7	6
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Swelling			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	3 / 3 (100.00%)	12 / 12 (100.00%)	9 / 9 (100.00%)
occurrences (all)	7	20	13
Hypothermia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Choking			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Cough			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Pneumothorax			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nasal obstruction			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Rhinitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Rales			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Use of accessory respiratory muscles			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Snoring			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	3 / 9 (33.33%)
occurrences (all)	0	3	3
Investigations			
Breath sounds abnormal			
subjects affected / exposed	2 / 3 (66.67%)	9 / 12 (75.00%)	7 / 9 (77.78%)
occurrences (all)	5	17	12
Viral test positive			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Oxygen saturation decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Endotracheal intubation complication			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Pneumocephalus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Thermal burn			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Tooth avulsion			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Transfusion reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Wound complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Wound			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Congenital, familial and genetic disorders			

Developmental hip dysplasia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Laryngomalacia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	3	2
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	3 / 3 (100.00%)	8 / 12 (66.67%)	5 / 9 (55.56%)
occurrences (all)	3	8	5
Dystonia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Irregular sleep phase			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)	4 / 9 (44.44%)
occurrences (all)	0	4	4
Eosinophilia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Dental caries			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Faecaloma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Gingival bleeding			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Regurgitation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Stress ulcer			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 3 (66.67%)	5 / 12 (41.67%)	3 / 9 (33.33%)
occurrences (all)	2	6	4
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2

Dermatitis diaper			
subjects affected / exposed	1 / 3 (33.33%)	3 / 12 (25.00%)	2 / 9 (22.22%)
occurrences (all)	1	3	2
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Rash			
subjects affected / exposed	1 / 3 (33.33%)	3 / 12 (25.00%)	2 / 9 (22.22%)
occurrences (all)	1	3	2
Musculoskeletal and connective tissue disorders			
Joint range of motion decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	3 / 9 (33.33%)
occurrences (all)	0	3	3
Conjunctivitis			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Gingivitis			
subjects affected / exposed	1 / 3 (33.33%)	4 / 12 (33.33%)	3 / 9 (33.33%)
occurrences (all)	1	4	3
Norovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 12 (33.33%)	3 / 9 (33.33%)
occurrences (all)	1	5	4
Pneumonia mycoplasmal			

subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 3 (66.67%)	9 / 12 (75.00%)	7 / 9 (77.78%)
occurrences (all)	4	14	10
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	- Information regarding the status of Studies AADC-CU/1601 and AADC-010 was updated. - Inclusion criteria were revised to specify that the participant was to be over 2 years old or have a skull thick enough for surgery and be under 6 years old prior to treatment with study drug. - Exclusion criteria were revised to specify that prohibition of taking any medications that may have affected the clinical trial does not apply to those drugs used at specified duration as mentioned in the protocol. - Timing of visits that required hospitalization was specified. - Eligible age of participants to receive 1.8 x 10^11 vg was changed from '≥3 years' to '>3 years' - Text regarding analysis of CSF fluid for L-3, 4-dihydroxyphenylalanine, 3-O-methyldopa, dopamine and serotonin was removed. - The assessments of motor function and development (PDMS-2, AIMS and Bayley-III) were described in more detail. - Items and schedules of treatment and examinations were updated for the screening, baseline examination, dosing day, 7-day post-treatment and 3-, 6-, 9-, and 12-month post-treatment time points. The table displaying the schedule of study procedures was also updated accordingly. A table of vital signs was added. - Specified for participants withdrawing from the trial (early termination), an overall evaluation with test items at 12 months would be required. - List of principal and sub-investigators was updated. - Time point of the magnetic resonance imaging performed post-treatment was specified to be 7 days (±7 days) post-surgery. - Number of participants in clinical trials to date for which gene therapy-induced dyskinesia was observed was updated from 8 to 18 participants. - Number of expected participants to be recruited was changed from 5 to 6 throughout where applicable. - Duration of the trial was updated to 14 months, including 28 days for pre-operative baseline examinations and 13 months for post-operative observations, throughout where applicable.
16 May 2017	- The period for recording oculogyric crises was changed from 28 days before gene therapy to the third month after gene therapy (previously 12 months post gene therapy). - The sponsor was updated from N/A to the National Taiwan University Hospital.
26 July 2017	- The aim of the trial was updated to include a slight increase in dose. - The number of participants expected to be recruited was updated to 10. - Enrollment of participants was allocated to 2 cohorts: cohort 1 (6 who were already treated or had their surgery date scheduled) and cohort 2 (4 planned to be treated with the 2.4 x 10^11 vg dose). For cohort 1, a summary of cases and a summary of post-gene therapy dyskinesia were included. - It was specified that either of 2 doses (1.8 x 10^11 vg or 2.4 x 10^11 vg) were administered in this study. - The text was updated to include 10 participants. • The duration for recording episodes of oculogyric crises was updated to: 28 days pre-surgery to 3 months post-surgery in-text and in the 'Summary of items and schedules of treatment and examination' table - Information about the long-term follow-up program after 12 months post-surgery was added. - Information about the Safety Committee was updated, including specifying that an external statistician would be included, and that the committee would meet once every 6 months to review adverse event reports related to significant events.
25 February 2020	- The text was updated to include 12 participants in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: