

**Clinical trial results:  
Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1  
Delivering AVXS-101  
Summary**

EudraCT number	2020-001235-27
Trial protocol	Outside EU/EEA
Global end of trial date	14 December 2017

**Results information**

Result version number	v1
This version publication date	11 August 2021
First version publication date	11 August 2021

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

Sponsor protocol code	AVXS-101-CL-101
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02122952
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Novartis Gene Therapies, Inc.
Sponsor organisation address	2275 Half Day Road, Bannockburn, IL, United States, 60015
Public contact	Novartis Gene Therapies EU Ltd., EMEA Medical Information, +353 (1) 566-2364, medinfoEMEA.gtx@novartis.com
Scientific contact	Novartis Gene Therapies EU Ltd., EMEA Medical Information, +353 (1) 566-2364, medinfoEMEA.gtx@novartis.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002168-PIP01-17
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	14 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 December 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the safety and efficacy of intravenous delivery of AVXS-101 as a treatment of spinal muscular atrophy Type 1 (SMN1).

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and were consistent with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	15
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)	2
Infants and toddlers (28 days-23 months)	13
Children (2-11 years)	0
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:

A total of 15 participants took part in the trial at a single site in the United States between May 2014 and December 2017.

### Pre-assignment

Screening details:

The study was designed to include 4 sequential dosing cohorts (Cohorts 1, 2A, 2B and 3). The study did not escalate to Cohort 3 as planned and Cohort 2A and 2B were combined and referred to as Cohort 2.

### 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
<b>Arm title</b>	Cohort 1

Arm description:

$6.7 \times 10^{13}$  vector gram per kilogram (vg/kg) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.

Arm type	Experimental
Investigational medicinal product name	AVXS-101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AVXS-101 was administered as an intravenous (IV) infusion over 60 minutes at a dose of  $6.7 \times 10^{13}$  vg/kg as assessed using quantitative polymerase chain reaction (qPCR).

<b>Arm title</b>	Cohort 2
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Arm description:

$2.0 \times 10^{14}$  vector gram per kilogram (vg/kg) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.

Arm type	Experimental
Investigational medicinal product name	AVXS-101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AVXS-101 was administered as an intravenous (IV) infusion over 60 minutes at a dose of  $2.0 \times 10^{14}$  vg/kg.

When measured initially by a qPCR assay, the Cohort 2 dose was assessed as  $2.0 \times 10^{14}$  vg/kg. Subsequently the Cohort 2 dose was directly measured by a more developed and further validated droplet digital polymerase chain reaction (ddPCR) method to be  $1.1 \times 10^{14}$  vg/kg. The dose is subsequently referred to as  $2.0 \times 10^{14}$  vg/kg throughout the following results.

<b>Number of subjects in period 1</b>	Cohort 1	Cohort 2
Started	3	12
Completed	3	12

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1
Reporting group description:	
6.7 X 10 <sup>13</sup> vector gram per kilogram (vg/kg) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.	
Reporting group title	Cohort 2
Reporting group description:	
2.0 X 10 <sup>14</sup> vector gram per kilogram (vg/kg) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.	

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	3	12	15
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	2	2
Infants and toddlers (28 days-23 months)	3	10	13
Children (2-11 years)	0	0	0
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: months			
arithmetic mean	6.3	3.4	
standard deviation	± 0.75	± 2.06	-
Gender categorical			
Units: Subjects			
Female	2	7	9
Male	1	5	6
Race			
Units: Subjects			
White	3	11	14
Other	0	1	1
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	3	10	13
Hispanic or Latino	0	2	2
Survival of motor neuron 2 (SMN2) copy number = 2			
Units: Subjects			
SMN2 copy number = 2	3	12	15
Bi-allelic deletions of SMN1			
Units: Subjects			
Bi-allelic deletions of SMN1	3	12	15

Exon 7 gene modifier mutation			
Units: Subjects			
Exon 7 gene modifier mutation	3	12	15

## End points

### End points reporting groups

Reporting group title	Cohort 1
Reporting group description: 6.7 X 10 <sup>13</sup> vector gram per kilogram (vg/kg) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.	
Reporting group title	Cohort 2
Reporting group description: 2.0 X 10 <sup>14</sup> vector gram per kilogram (vg/kg) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.	

### Primary: Number of Participants Who Experienced a Treatment-related Unacceptable Toxicity

End point title	Number of Participants Who Experienced a Treatment-related Unacceptable Toxicity <sup>[1]</sup>
End point description: Unacceptable toxicity was defined as one grade III or higher unanticipated, treatment-related toxicity that presented with clinical symptoms and required medical treatment.	
End point type	Primary
End point timeframe: Up to 24 months post-dose	

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: No comparative analyses were planned.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: Participants	1	3		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Who Experienced Permanent Ventilation or Death

End point title	Number of Participants Who Experienced Permanent Ventilation or Death
End point description: Permanent ventilation was defined as the requirement of $\geq 16$ -hour respiratory assistance, including non-invasive ventilatory support, per day continuously for $\geq 2$ weeks in the absence of an acute reversible illness, excluding perioperative ventilation.	
End point type	Secondary
End point timeframe: Up to 13.6 months of age	

<b>End point values</b>	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: Participants	0	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) Score by Visit

End point title	Mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) Score by Visit
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End point description:

Score ranges from 0 to 64, where 64 is the maximum possible score. A higher score is indicative of higher/better motor function. CHOP-INTEND assessments were discontinued once patients achieved higher functioning status, so the number of available data points decreased over time.

Number of Participants Evaluated in Cohort 1:

For baseline and months 1, 2, 3, 4, 5, 6 and 7, N = 3

Months 8, 9, 10, 12, 13, 14 and 17, N = 2

Months 11, 15, 16, 18, 19 and 20, N = 1

Month 24, N = 0

Number of Participants Evaluated in Cohort 2 :

For baseline and months 1 and 3, N = 12

Months 2, 4, 5, 6 and 11 N = 11

Months 8, 9 and 10, N = 10

Months 7 and 12, N = 9

Month 13 and 15 N = 7

Months 18 and 24 N = 6

Month 16 and 17 N = 5

Month 14, N = 3

Months 19 and 20, N = 2

99999 = no estimable data. Mean was not estimable where N = 0. Standard deviation was not estimable where N = 0 or N = 1.

End point type	Secondary
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End point timeframe:

Baseline up to 24 months post-dose

<b>End point values</b>	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Baseline	16.3 (± 10.50)	28.2 (± 12.29)		
Month 1	16.7 (± 11.02)	37.9 (± 12.72)		
Month 2	15.7 (± 10.50)	42.8 (± 13.36)		
Month 3	16.0 (± 8.00)	43.6 (± 13.47)		
Month 4	18.0 (± 9.00)	46.8 (± 13.55)		
Month 5	18.3 (± 11.24)	50.7 (± 8.59)		
Month 6	20.7 (± 12.58)	49.5 (± 13.95)		
Month 7	19.7 (± 12.58)	52.3 (± 7.98)		
Month 8	25.0 (± 8.49)	49.2 (± 13.94)		
Month 9	16.0 (± 8.49)	54.6 (± 6.29)		
Month 10	21.5 (± 14.85)	53.8 (± 5.57)		
Month 11	9.0 (± 99999)	49.5 (± 12.21)		
Month 12	19.5 (± 16.26)	53.6 (± 5.53)		
Month 13	14.5 (± 7.78)	53.7 (± 6.40)		
Month 14	16.0 (± 5.66)	53.7 (± 2.31)		
Month 15	10.0 (± 99999)	56.1 (± 2.67)		
Month 16	29.0 (± 99999)	52.0 (± 4.80)		
Month 17	21.5 (± 10.61)	53.6 (± 5.41)		
Month 18	36.0 (± 99999)	55.7 (± 3.72)		
Month 19	37.0 (± 99999)	58.5 (± 0.71)		
Month 20	15.0 (± 99999)	57.0 (± 1.41)		
Month 24	99999 (± 99999)	55.5 (± 1.76)		

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Participants Who Achieved Functional Independent Sitting

End point title	Number of Participants Who Achieved Functional Independent Sitting
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End point description:

Achievement of functional independent sitting was defined as the ability to maintain a sitting position independently for at least 30 seconds as confirmed per video evaluation by an expert central reviewer based on videos taken either at scheduled visits or provided by the parent/legal guardian.

End point type	Other pre-specified
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End point timeframe:

Up to 24 months post-dose

<b>End point values</b>	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: Participants	0	9		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 months post-dose

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

6.7 X 10<sup>13</sup> vg/kg of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.

Reporting group title	Cohort 2
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Reporting group description:

2.0 X 10<sup>14</sup> vg/kg of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein.

<b>Serious adverse events</b>	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	10 / 12 (83.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Enterovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory failure</b>			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Adenovirus infection</b>			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bronchitis</b>			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Enterovirus infection</b>			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastroenteritis</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastroenteritis viral</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Influenza</b>			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Lower respiratory tract infection</b>			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	7 / 12 (58.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			

subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	12 / 12 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site dermatitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Catheter site inflammation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Pyrexia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	7 / 12 (58.33%) 12	
Secretion discharge subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Immune system disorders			
Food allergy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Aspiration subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Atelectasis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 12 (25.00%) 3	
Cough subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	5 / 12 (41.67%) 11	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 2	
Epistaxis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Hypoxia		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Nasal congestion		
subjects affected / exposed	0 / 3 (0.00%)	6 / 12 (50.00%)
occurrences (all)	0	9
Nasal oedema		
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	0
Pleural effusion		
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	0
Respiratory failure		
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	5
Respiratory tract congestion		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	2
Rhinitis allergic		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Rhinorrhoea		
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	4
Snoring		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Tachypnoea		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Upper respiratory tract congestion		
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	0
Wheezing		

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 12 (16.67%) 2	
<b>Investigations</b>			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Enterovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Eosinophil count increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Human rhinovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
<b>Injury, poisoning and procedural complications</b>			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	3	
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Humerus fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Lower limb fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Mouth injury			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Procedural pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Tibia fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Traumatic haematoma subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Wound subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Tachycardia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 3	
Ventricular hypertrophy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 2	
Chalazion subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 12 (0.00%) 0	
Dry eye			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Gastrointestinal disorders</b>			
<b>Abdominal distension</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Abdominal pain</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Constipation</b>			
subjects affected / exposed	1 / 3 (33.33%)	6 / 12 (50.00%)	
occurrences (all)	1	8	
<b>Diarrhoea</b>			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	3	
<b>Dysphagia</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Gastric hypomotility</b>			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
<b>Gastroesophageal reflux disease</b>			
subjects affected / exposed	1 / 3 (33.33%)	5 / 12 (41.67%)	
occurrences (all)	1	6	
<b>Haematemesis</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Haematochezia</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Hiatus hernia</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
<b>Nausea</b>			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Teething			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	8 / 12 (66.67%)	
occurrences (all)	0	11	
<b>Skin and subcutaneous tissue disorders</b>			
Acne infantile			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Dermatitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 3 (33.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Excessive granulation tissue			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	
occurrences (all)	0	6	
Rash generalised			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin discolouration			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Urticaria subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 12 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Mastication disorder subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Muscular weakness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Osteopenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Scoliosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Infections and infestations			
Alpha haemolytic streptococcal infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Bronchiolitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 12 (25.00%) 3	
Catheter site cellulitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 12 (0.00%) 0	
Clostridium difficile colitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 12 (16.67%) 2	
Ear infection			

subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	2
Enterovirus infection		
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	5
Gastroenteritis viral		
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	4
Influenza		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	2
Metapneumovirus infection		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Oral candidiasis		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Otitis externa		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	2 / 3 (66.67%)	2 / 12 (16.67%)
occurrences (all)	6	3
Otitis media acute		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Parainfluenzae virus infection		
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	2
Pharyngitis		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Pharyngitis streptococcal		

subjects affected / exposed	1 / 3 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	2
Pneumonia		
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	4
Pneumonia viral		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Pseudomonas infection		
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	0
Respiratory tract infection		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Rhinovirus infection		
subjects affected / exposed	1 / 3 (33.33%)	4 / 12 (33.33%)
occurrences (all)	1	5
Staphylococcal bacteraemia		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Staphylococcal infection		
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	0
Tonsillitis		
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	1 / 3 (33.33%)	10 / 12 (83.33%)
occurrences (all)	3	28
Urinary tract infection		
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	2
Viral infection		
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Viral upper respiratory tract infection		

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 12 (16.67%) 2	
Wound infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Metabolism and nutrition disorders			
Dehydration subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	
Fluid overload subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 2	
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 3	0 / 12 (0.00%) 0	
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 12 (8.33%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2014	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• CHOP-INTEND and Ability Captured Through Interactive Video Evaluation – mini (ACTIVE-mini) assessed at additional time points</li> <li>• Urine, saliva, and feces sample collections added for future research of viral shedding</li> <li>• Blood sample collected at Day 60 to assess serum antibody, T-cell response (ELISpot), and for future research</li> <li>• Treat patients with positive T-cell immune response with prednisolone (1 to 2 mg/kg once daily) and close monitoring of T-cell immune reaction</li> </ul>
24 July 2014	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Safety laboratory assessments collected at additional time points</li> <li>• Direct bilirubin and albumin added to safety laboratory analyses</li> <li>• Immunology (anti-AAV9/SMN antibody and T-cells), research blood, and urinalysis collected at additional time points</li> <li>• Added vaccination recommendations</li> <li>• Prednisolone treatment changed to approximately 1 mg/kg once per day starting prophylactically 1 day prior to AVXS-101 infusion with a tapering protocol based on immune response to AVXS-101 <ul style="list-style-type: none"> <li>o Dose could have been increased to approximately 2 mg/kg once per day, depending on T-cell response measured by ELISpot assay</li> </ul> </li> <li>• Administer AVXS-101 within 8 hours of preparation</li> </ul>
08 October 2014	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Intermediate dose of <math>2.0 \times 10^{14}</math> vg/kg Cohort 2 (n=3) added</li> <li>• High dose of <math>3.3 \times 10^{14}</math> vg/kg moved to Cohort 3 (n=3)</li> </ul>
20 January 2015	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Secondary objective of study revised to the time from birth until death or time to <math>\geq 16</math>-hour respiratory assistance continuously for <math>\geq 2</math> weeks in the absence of an acute reversible illness</li> <li>• Maintain prophylactic prednisolone treatment for <math>\leq 30</math> days</li> <li>• Revised prednisolone tapering schedule to be based on interferon-gamma T-cell response and aspartate aminotransferase/alanine aminotransferase values</li> <li>• Request permission for autopsy at time of death</li> </ul>
12 March 2015	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Primary objective of study revised to determination of safety based on the development of unacceptable toxicity: defined as the occurrence of any one Grade 3 or higher, unanticipated, treatment-related toxicity</li> <li>• Cohort 2 to include <math>\geq 3</math> and <math>\leq 6</math> patients and Cohort 3 to include up to 3 patients</li> <li>• Prednisolone did not need to be maintained for <math>\leq 30</math> days and revised tapering schedule</li> <li>• Research urine, saliva, and stool assessed at additional time points</li> <li>• Replace AE severity classifications with Common Terminology Criteria for Adverse Events (CTCAE) v4.03 classifications (Grades 1 to 5)</li> <li>• Severity of liver toxicity assessed using NIH Guideline for Severity Grading in Drug Induced Liver Injury (Grades 1 to 5), including assessments of association or relatedness to AVXS-101</li> <li>• Required dose level toxicities to be unanticipated</li> <li>• Saliva, urine, and stool research samples collected at additional time points</li> </ul>

04 May 2015	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Bayley Scales added to exploratory outcome measures with fine and gross motor subtests administered to patients who achieved CHOP-INTEND scores <math>\geq 60</math></li> <li>• Research urine assessed at additional time point</li> <li>• Removed severity of liver toxicity grading added in Protocol v11.0</li> <li>• Stopping criteria required Grade 3 or higher AE toxicity, clinical symptoms, and medical treatment</li> </ul>
10 June 2015	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Removed Cohort 3 and Cohort 2 renamed Cohort 2A</li> <li>• Extended enrollment to 6 additional patients (intermediate dose) following gene transfer of first 9 patients</li> <li>• Addendum 2, v1.0 (24Jun2015) <ul style="list-style-type: none"> <li>◦ Expand sample size with Cohort 2B (2.0E14 vg/kg) and added Cohort 3 (3.3E14 vg/kg), each consisting of 3 patients</li> <li>◦ The age of patients on the day of AVXS-101 infusion was decreased to 6 months of age or younger for Cohort 2B and Cohort 3</li> </ul> </li> </ul>
21 April 2016	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Added secondary objective of change from baseline in CHOP-INTEND score, and improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted <ul style="list-style-type: none"> <li>◦ Additionally, AveXis could provide videos of the physical exams, CHOP-INTEND assessments, and/or Bayley Scales assessments to an independent, blinded reviewer for confirmation of the development milestones</li> </ul> </li> <li>• Added objective of compelling, demonstrable, documented evidence of efficacy as determined by changes in functional abilities as captured during videotaping sessions during site visits and/or captured by patient/parent/legal guardian at home</li> <li>• Added primary analysis for efficacy assessed when all patients reach 13.6 months of age, and follow-up safety analysis completed when the last patient reaches 24 months post-dose</li> <li>• Initial genetic testing and diagnosis could be completed by a different institution/laboratory and could be confirmed by AveXis through a third-party laboratory using an additional blood sample</li> <li>• Updates and clarifications to CHOP-INTEND requirements</li> <li>• Bayley Scales fine motor, gross motor, and cognition subtests administered for CHOP-INTEND scores <math>\geq 60</math></li> <li>• During the first year, Bayley Scales gross and fine motor subtests assessed monthly, and cognition subtest assessed every 3 months. During the second year, all Bayley Scales subtests assessed every 3 months, except for patients being seen monthly for CHOP-INTEND assessments. For these patients, the first year assessment schedule was followed.</li> <li>• Assess the age at which significant motor milestones achieved using the Motor Milestone Development Survey and Gross Motor Skills Checklist.</li> </ul>
21 November 2016	<p>The following change was made:</p> <ul style="list-style-type: none"> <li>• This Institutional Review Board-approved amended protocol, which added a co-primary endpoint and secondary endpoints, was rescinded 23Jan2017, in response to feedback received from the FDA suggesting the objectives and endpoints set forth in Protocol dated 21Apr2016 be maintained due to the open-label nature of the study</li> </ul>
23 January 2017	<p>The following change was made:</p> <ul style="list-style-type: none"> <li>• Quarterly instead of monthly visits during the second year</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported