Clinical trial results:
A Global Study of a Single, One-Time Dose of AVXS-101 Delivered to Infants with Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy with Multiple Copies of SMN2

Summary

EudraCT number	2017-004087-35
Trial protocol	ES IT GB BE NL
Global end of trial date	15 June 2021

Results information

Result version number	v1
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	AVXS-101-CL-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03505099
WHO universal trial number (UTN)	-
Other trial identifiers	JapicCTI: JapicCTI-184203

Notes:

Sponsors

Sponsor organisation name	Novartis Gene Therapies EU Limited
Sponsor organisation address	2275 Half Day Road, Bannockburn, IL, United States, 60015
Public contact	EMEA Medical Information, Novartis Gene Therapies, Inc., +353 (1) 566-2364, medinfoemea.gtx@novartis.com
Scientific contact	EMEA Medical Information, Novartis Gene Therapies, Inc., +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)	EMEA-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	15 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were to:
• Cohort 1 - Assess the efficacy of AVXS-101 by demonstrating functional independent sitting for at least 30 seconds as defined by the Bayley Scales of Infant and Toddler Development (BSID) gross motor (GM) subtest item number 26 at any visit up to 18 months of age.
• Cohort 2 - Assess the efficacy of AVXS-101 based on the proportion of participants achieving the ability to stand without support for at least 3 seconds as defined by BSID GM subtest item number 40 at any visit up to 24 months of age.

Protection of trial subjects:

The study was conducted according to International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
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: 20
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 1
Worldwide total number of subjects	30
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	17
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 44 participants were screened, of which 14 were screen failures and 30 were enrolled and received study drug. A total of 30 participants took part in the trial at 16 sites in the United States, the United Kingdom, Belgium, Canada, Australia and Japan between April 2018 and June 2021.

Pre-assignment

Screening details:

One participant was initially diagnosed as having 3 copies of survival of motor neuron 2 (SMN2) and was enrolled into Cohort 2, but a re-confirmation test reported post-dose showed 4 copies of SMN2. This participant was excluded from all analysis populations and data is not reported due to privacy concerns.

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	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2

Arm description:

Participants with bi-allelic deletions of survival of motor neuron 1 (SMN1) and 2 copies of SMN2 received a single dose of AVXS-101 administered as an intravenous (IV) infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

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 IV infusion over 60 minutes at a dose of 1.1 × 10^14 vg/kg (vector genome per kilogram).

Arm title	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2

Arm description:

Participants with bi-allelic deletions of SMN1 and 3 copies of SMN2 received a single dose of AVXS-101 administered as an IV infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

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 IV infusion over 60 minutes at a dose of 1.1 × 10^14 vg/kg.

Number of subjects in period 1[1]	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2
Started	14	15
Received AVXS-101	14	15
Completed	14	15

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant was initially diagnosed as having 3 copies of SMN2 and was enrolled into Cohort 2, but a re-confirmation test reported post-dose showed 4 copies of SMN2. This participant was excluded from all analysis populations and data is not reported due to privacy concerns.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2
Reporting group description:	
Participants with bi-allelic deletions of survival of motor neuron 1 (SMN1) and 2 copies of SMN2 received a single dose of AVXS-101 administered as an intravenous (IV) infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.	
Reporting group title	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2
Reporting group description:	
Participants with bi-allelic deletions of SMN1 and 3 copies of SMN2 received a single dose of AVXS-101 administered as an IV infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.	

Reporting group values	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2	Total
Number of subjects	14	15	29
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	11	6	17
Infants and toddlers (28 days-23 months)	3	9	12
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
Gender categorical Units: Subjects			
Female	10	9	19
Male	4	6	10
Ethnicity Units: Subjects			
Hispanic or Latino	4	2	6
Not Hispanic or Latino	10	13	23
Unknown or Not Reported	0	0	0
Race Units: Subjects			
Asian	2	2	4
American Indian or Alaska Native	0	1	1
Black or African American	1	0	1
White	7	10	17
Other	4	2	6

SMN2 gene modifier mutation (c.859G>C) Units: Subjects			
SMN2 gene modifier mutation (c. 859G>C) Present	0	0	0
SMN2 gene modifier mutation (c. 859G>C) Absent	14	15	29

End points

End points reporting groups

Reporting group title	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2

Reporting group description:

Participants with bi-allelic deletions of survival of motor neuron 1 (SMN1) and 2 copies of SMN2 received a single dose of AVXS-101 administered as an intravenous (IV) infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2

Reporting group description:

Participants with bi-allelic deletions of SMN1 and 3 copies of SMN2 received a single dose of AVXS-101 administered as an IV infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Primary: Cohort 1: Number of Participants Who Achieved Sitting Alone for at Least 30 Seconds

End point title	Cohort 1: Number of Participants Who Achieved Sitting Alone for at Least 30 Seconds[1][2]

End point description:

Defined by the Bayley Scales of Infant and Toddler Development (BSID) Gross Motor (GM) subtest performance criteria number 26, confirmed by video recording, as a participant who sits for at least 30 seconds without assistance from another person or object. The participant was allowed to use their upper extremities.

The analysis population was the Intent-to-Treat (ITT) population (cohort 1) which included all enrolled participants with bi-allelic SMN1 deletions and 2 copies of SMN2 without the SMN2 gene modifier mutation (c.859G>C) who received AVXS-101.

End point type	Primary

End point timeframe:

From Day 1 up to 18 months of age visit

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 statistical analyses were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was only collected for participants in Cohort 1.

End point values	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 2: Cohort 2: Number of Participants Who Achieved Standing Alone for at Least 3 Seconds

End point title	Cohort 2: Cohort 2: Number of Participants Who Achieved Standing Alone for at Least 3 Seconds[3][4]

End point description:

Defined by the BSID GM subtest performance criteria number 40, confirmed by video recording, as a participant who stands alone for at least 3 seconds unsupported.

The analysis population was the ITT population (cohort 2) which included all enrolled participants with bi-allelic SMN1 deletions and 3 copies of SMN2 without the SMN2 gene modifier mutation (c.859G>C) who received AVXS-101.

End point type	Primary

End point timeframe:

From Day 1 up to 24 months of age visit

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: No comparative statistical analyses were planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was only collected for participants in Cohort 2.

End point values	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Event-free Survival at 14 Months of Age

End point title	Cohort 1: Event-free Survival at 14 Months of Age[5]

End point description:

Event-free survival at 14 months of age was defined as the number of participants who did not die, did not require permanent ventilation and did not withdraw from the study by 14 months of age.

The analysis population was the ITT population (cohort 1) which included all enrolled participants with bi-allelic SMN1 deletions and 2 copies of SMN2 without the SMN2 gene modifier mutation (c.859G>C) who received AVXS-101.

End point type	Secondary

End point timeframe:

From Day 1 up to 14 months of age

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was only collected for participants in Cohort 1.

End point values	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Number of Participants Who Achieved the Ability to Maintain Weight at or Above the Third Percentile Without the Need for Non-Oral or Mechanical Feeding Support

End point title	Cohort 1: Number of Participants Who Achieved the Ability to Maintain Weight at or Above the Third Percentile Without the Need for Non-Oral or Mechanical Feeding Support[6]

End point description:

The ability to maintain weight at or above the third percentile without the need for non-oral or mechanical feeding support was defined by meeting the following criteria at each visit up to 18 months of age:
• Did not receive nutrition through mechanical support (i.e., feeding tube)
• Maintained weight (≥ third percentile for age and sex as defined by World Health Organization [WHO] guidelines) consistent with the participant's age at the assessment.

The analysis population was the ITT population (cohort 1) which included all enrolled participants with bi-allelic SMN1 deletions and 2 copies of SMN2 without the SMN2 gene modifier mutation (c.859G>C) who received AVXS-101.

End point type	Secondary

End point timeframe:

From Day 1 up to 18 months of age

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was only collected for participants in Cohort 1.

End point values	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2: Number of Participants Who Achieved the Ability to Walk Alone

End point title	Cohort 2: Number of Participants Who Achieved the Ability to Walk Alone[7]

End point description:

Defined by the BSID GM subtest performance criteria number 43, confirmed by video recording, as a participant who takes 5 coordinated independent steps.

The analysis population was the ITT population (cohort 2) which included all enrolled participants with bi-allelic SMN1 deletions and 3 copies of SMN2 without the SMN2 gene modifier mutation (c.859G>C) who received AVXS-101.

End point type	Secondary

End point timeframe:

From Day 1 up to 24 months of age visit

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was only collected for participants in Cohort 2.

End point values	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Cohort 1: Treatment-emergent adverse events (TEAEs) were collected from Day 1 up to 18 months of age.
Cohort 2: TEAEs were collected from Day 1 up to 24 months of age.

Adverse event reporting additional description:

Serious adverse events (SAEs) were collected from signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 20 months for Cohort 1 and 26 months for Cohort 2).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2

Reporting group description:

Participants with bi-allelic deletions of survival of motor neuron 1 (SMN1) and 2 copies of SMN2 received a single dose of AVXS-101 administered as an intravenous (IV) infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2

Reporting group description:

Participants with bi-allelic deletions of SMN1 and 3 copies of SMN2 received a single dose of AVXS-101 administered as an IV infusion over 60 minutes on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Serious adverse events	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	3 / 15 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Middle ear effusion			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Croup infectious			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: Bi-allelic Deletions of SMN1 and 2 Copies of SMN2	Cohort 2: Bi-allelic Deletions of SMN1 and 3 Copies of SMN2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	15 / 15 (100.00%)	
General disorders and administration site conditions			
Developmental delay			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	7 / 14 (50.00%)	11 / 15 (73.33%)	
occurrences (all)	7	18	
Vessel puncture site bruise			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	4 / 15 (26.67%)	
occurrences (all)	4	6	
Nasal congestion			

subjects affected / exposed	3 / 14 (21.43%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Snoring			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	2	
Agitation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	3 / 15 (20.00%)	
occurrences (all)	2	5	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 14 (21.43%)	4 / 15 (26.67%)	
occurrences (all)	4	6	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Head lag			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Platelet count increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Troponin increased			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Bacterial test positive			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood calcium increased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Carbon dioxide decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Eye injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Tracheal deviation			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Arthropod sting			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eyelid injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin wound			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Dacryostenosis congenital			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Hydrocele			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Areflexia			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Hypertonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypokinesia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hyporeflexia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypotonia			
subjects affected / exposed	3 / 14 (21.43%)	2 / 15 (13.33%)	
occurrences (all)	5	3	
Motor developmental delay			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Muscle contractions involuntary			
subjects affected / exposed	3 / 14 (21.43%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Tremor			
subjects affected / exposed	3 / 14 (21.43%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Febrile convulsion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Microcytic anaemia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Thrombocytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Middle ear effusion			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Eye disorders			
Eye discharge			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Chalazion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	4 / 14 (28.57%)	1 / 15 (6.67%)	
occurrences (all)	5	1	
Diarrhoea			
subjects affected / exposed	3 / 14 (21.43%)	4 / 15 (26.67%)	
occurrences (all)	4	5	
Dysphagia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 14 (21.43%)	3 / 15 (20.00%)	
occurrences (all)	3	4	
Gingival pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Inguinal hernia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Teething			
subjects affected / exposed	2 / 14 (14.29%)	5 / 15 (33.33%)	
occurrences (all)	2	6	
Tooth development disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 14 (21.43%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haematemesis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Regurgitation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Cafe au lait spots			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Eczema			
subjects affected / exposed	2 / 14 (14.29%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	3 / 14 (21.43%)	2 / 15 (13.33%)	
occurrences (all)	6	2	
Blister			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dermatitis diaper			
subjects affected / exposed	0 / 14 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Eczema infantile			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lipohypertrophy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Miliaria			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nephrocalcinosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pyelocaliectasis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Dysuria			

subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Endocrine disorders			
Precocious puberty			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Cushingoid			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Hip deformity			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Joint contracture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Kyphosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Loose body in joint			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Candida nappy rash			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Croup infectious			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	3	3	
Fungal infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Infected bite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	2 / 14 (14.29%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	2 / 14 (14.29%)	3 / 15 (20.00%)	
occurrences (all)	3	4	
Otitis media			
subjects affected / exposed	1 / 14 (7.14%)	3 / 15 (20.00%)	
occurrences (all)	1	6	
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			

subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)		
occurrences (all)	1	2		
Rhinitis				
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)		
occurrences (all)	1	1		
Rhinovirus infection				
subjects affected / exposed	2 / 14 (14.29%)	0 / 15 (0.00%)		
occurrences (all)	2	0		
Upper respiratory tract infection				
subjects affected / exposed	5 / 14 (35.71%)	9 / 15 (60.00%)		
occurrences (all)	7	13		
Viral upper respiratory tract infection				
subjects affected / exposed	3 / 14 (21.43%)	1 / 15 (6.67%)		
occurrences (all)	10	1		
Bronchitis				
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
Exanthema subitum				
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
Fungal skin infection				
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
Gastroenteritis				
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)		
occurrences (all)	0	3		
Hand-foot-and-mouth disease				
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)		
occurrences (all)	0	2		
Otitis media acute				
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
Respiratory syncytial virus infection				
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		

Roseola			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Lactose intolerance			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Poor feeding infant			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Weight gain poor			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2018	Global version 2.0 - Amendment 1 Updated to include recent good laboratory practice toxicology data, to provide additional cardiac monitoring for participant safety, to allow laboratory samples to be processed locally in certain instances, and added Japan participant urine, saliva and stool collections for viral shedding analysis. Cohort 3 for participants with 4 copies of SMN2 removed leading to changes in objectives, investigational plan, selection criteria, assessments of efficacy and safety, and statistical analysis. Amendment 1 was not submitted to Institutional Review Board /Independent Ethics Committee or regulatory agencies because Amendment 2 was already planned and was submitted as soon as Global Version 1.0 was approved (in countries where it had been submitted).
19 October 2018	Global Version 3.0 - Amendment 2 Included the changes outlined above for Amendment 1. In addition, updated to provide a correction to the timing of genetic reconfirmation testing from Month 3 to screening and revisions for consistency across AVXS-101 protocols. Additional cardiac monitoring (24-hour Holter monitoring, electrocardiogram [ECG], and echocardiogram [ECHO]) were added to assure participant safety.
30 May 2019	Global Version 4.0 - Amendment 3 Updated to include a new regimen for prophylactic prednisolone and additional visits for liver function test monitoring according to recommendations made by Sponsor following acute liver failure case reported in the United States Managed Access Program. Updates related to additional toxicology biodistribution studies, release of AVXS-101-CL-101 clinical study report. Safety reporting and analysis, and removal of Japan specific assessments which were included in a separate, Japan-specific protocol.
26 November 2019	Global Version 5.0 - Amendment 4 Updates related to non-clinical recent dorsal root ganglia findings in cynomolgus monkeys to further clarify that detailed age appropriate sensory testing is performed during the neurological component of the physical exam. Adverse events of special interests in the areas of hepatotoxicity, thrombocytopenia, cardiac adverse events, and sensory abnormalities suggestive of ganglionitis were included in this protocol amendment.
28 July 2020	Global Version 6.0 - Amendment 5 Updates related to potential coronavirus disease 2019 (COVID-19) impact on trial conduct, consistency for definitions of the primary endpoints and exploratory endpoints, central review of videos for efficacy parameters, Safety Reporting timelines and addition Hy's Law Criteria due to request by Belgian Regulatory Authority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported