Clinical trial results:
Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion

Summary

EudraCT number	2020-000095-38
Trial protocol	Outside EU/EEA
Global end of trial date	12 November 2019

Results information

Result version number	v2 (current)
This version publication date	02 September 2022
First version publication date	22 May 2020
Version creation reason	• New data added to full data set New data to be added.

Trial information

Trial identification

Sponsor protocol code	AVXS-101-CL-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03306277
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AveXis, Inc
Sponsor organisation address	2275 Half Day Road, Bannockburn, United States, IL 60015
Public contact	EMEA Medical Information, AveXis Eu Ltd , +353 (1) 566-2364, medinfo.emea@avexis.com
Scientific contact	EMEA Medical Information, AveXis Eu Ltd , +353 (1) 566-2364, medinfo.emea@avexis.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2019
Global end of trial reached?	Yes
Global end of trial date	12 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Determine efficacy by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age visit.
• Determine the efficacy based on survival at 14 months of age. Survival is defined by avoidance of combined endpoint of either (a) death or (b) permanent ventilation.

Protection of trial subjects:

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AveXis' policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
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: 22
Worldwide total number of subjects	22
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)	1
Infants and toddlers (28 days-23 months)	21
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:

22 participants were recruited at 12 study centres in the United States.

Pre-assignment

Screening details:

A screening period of up to 30 days occurred before treatment.

Period 1

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

Arms

Arm title	AVXS-101

Arm description:

Single dose of AVXS-101 administered as an intravenous (IV) infusion.

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

Dosage and administration details:

Participants received a single dose of AVXS-101 as an intravenous (IV) infusion.

Number of subjects in period 1	AVXS-101
Started	22
Completed	19
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	1	1	
Infants and toddlers (28 days-23 months)	21	21	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
arithmetic mean	3.7		
standard deviation	± 1.6	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	10	10	
Race Units: Subjects			
White	11	11	
Black or African American	3	3	
Asian	2	2	
Other	6	6	
Ethnicity Units: Subjects			
Not Hispanic or Latino	18	18	
Hispanic or Latino	4	4	
Patient reported hospitalizations Units: Subjects			
Yes	17	17	
No	5	5	
Weight at baseline Units: kg			
arithmetic mean	5.8		
standard deviation	± 1.1	-	
Height/length at baseline Units: cm			

arithmetic mean	61.3		
standard deviation	± 4.3	-	

End points

End points reporting groups

Reporting group title	AVXS-101

Reporting group description:

Single dose of AVXS-101 administered as an intravenous (IV) infusion.

Subject analysis set title	PNCR (Historical Control)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in historical control PNCR cohort received uniform standard of care treatment. Participants visited the study site at baseline and at 2, 4, 6, 9, 12 months and every 6 months thereafter.

Primary: Achievement of independent sitting for at least 30 seconds

End point title	Achievement of independent sitting for at least 30 seconds[1]

End point description:

This endpoint is a co-primary endpoint.
Independent sitting is defined as sitting for at least 30 seconds at the 18 months of age visit.
A one-sided Exact Binomial Test was used to test the null hypothesis of p=0.1% at significance level of 0.025. The corresponding 97.5% confidence intervals was estimated by the exact method for binomial proportions. It was assumed that the true response rate for the primary endpoint was actually zero (or as low as 0.1%) in the population of historical control; the first co-primary efficacy endpoint hypothesis was that the AVXS-101 treated participants achieve a response rate greater than 0.1%.
The two co-primary efficacy endpoints were assessed in sequence: The endpoint of functional independent sitting was assessed first and, only when this assessment met statistical significance was the endpoint of survival assessed.

End point type	Primary

End point timeframe:

At 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: There are no statistical analyses associated with this endpoint.

End point values	AVXS-101			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Participants	13			

Statistical analyses

No statistical analyses for this end point

Primary: Event-free survival

End point title	Event-free survival[2]

End point description:

The endpoint is a co-primary endpoint.
Survival is defined by the avoidance of combined endpoint of either death or permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation is considered a surrogate for death. An acute reversible illness is defined as any condition other than SMA that results in increased medical intervention.
A two sample 2-sided Fischer's exact test was used to test the null hypothesis of p=historical at the

significance level of 0.05.
The two co-primary efficacy endpoints were assessed in sequence: The endpoint of functional independent sitting was assessed first and, only when this assessment met statistical significance was the survival endpoint assessed.

End point type	Primary

End point timeframe:

14 months of age

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical analyses associated with this endpoint.

End point values	AVXS-101			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Participants	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Ability to thrive

End point title	Ability to thrive

End point description:

This is a co-secondary endpoint.

Ability to thrive is defined as achieving all of the following at 18 months of age:
- does not receive nutrition through mechanical support or other non-oral method
- ability to tolerate thin liquids as demonstrated through a formal swallowing test
- maintains weight

The two co-secondary endpoints were assessed in sequence: The endpoint of ability to thrive was assessed first and, only when this assessment met statistical significance was the endpoint of ventilatory support independence assessed. Comparison to the historical was made using 0.1% as comparison, as the percentage of participants who maintained ability to thrive was essentially 0.

One-sided exact binomial tests were executed for secondary efficacy analyses on the Intent to Treat (ITT) population.

End point type	Secondary

End point timeframe:

At 18 months of age

End point values	AVXS-101			
Subject group type	Reporting group			
Number of subjects analysed	22[3]			
Units: Participants	9			

Notes:

[3] - Two participants discontinued the study prior to 18 months.

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilatory support independence

End point title	Ventilatory support independence

End point description:

This is a co-secondary endpoint.

Ventilatory support independence is defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, through assessment of actual usage data captured from the device (Phillips Trilogy).

The two co-secondary endpoints were assessed in sequence: The endpoint of ability to thrive was assessed first and, only when this assessment met statistical significance was the endpoint of ventilatory support independence assessed. Comparison to the historical was made using 0.1% as comparison, as the percentage of participants who maintained independence from ventilatory support was essentially 0.

One-sided exact binomial tests were executed for secondary efficacy analyses on the Intent to Treat (ITT) population.

Two participants had Trilogy data at or after 18 months of age.

End point type	Secondary

End point timeframe:

At 18 months

End point values	AVXS-101			
Subject group type	Reporting group			
Number of subjects analysed	22[4]			
Units: Participants	18			

Notes:

[4] - Two participants discontinued the study prior to 18 months.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Event-free Survival at 14 Months of Age Compared to Data From an Historical Control, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014

End point title	Event-free Survival at 14 Months of Age Compared to Data From an Historical Control, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014

End point description:

Data for the current study were compared to data from an historical control (PNCR. Finkel et al, 2014 - PubMed 25080519). 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.

End point type	Other pre-specified

End point timeframe:

14 months of age

End point values	AVXS-101	PNCR (Historical Control)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	22	23		
Units: participants	20	6		

Statistical analyses

Statistical analysis title	AVXS-101 versus PNCR

Statistical analysis description:

This comparison is made against the results from the age and gender-matched control participants selected from existing natural history data sets (PNCR) [Neurol. 2014; 83(9):810-817].

Comparison groups	AVXS-101 v PNCR (Historical Control)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 18 months of age	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1
Reporting groups	
Reporting group title	AVXS-101
Reporting group description: Single dose of AVXS-101 administered as an intravenous (IV) infusion.	

Serious adverse events	AVXS-101		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 22 (45.45%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Human metapneumovirus test positive			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			

subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Infections and infestations				
Bronchiolitis				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus bronchiolitis				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bacterial tracheitis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Abnormal weight gain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Feeding disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AVXS-101		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 22 (54.55%)		
occurrences (all)	26		
Reproductive system and breast disorders			
Use of accessory respiratory muscles			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	10		
Respiratory distress			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Respiration abnormal			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	6		
Nasal congestion			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Sleep apnoea syndrome			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Tachypnoea			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Respiratory track congestion			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Rhinorrhea			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Upper respiratory tract congestion			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	9		
Alanine aminotransferase increased			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	8		
Blood creatine phosphokinase MB increased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Lymphocyte count decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Arthropod bite			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	7		

Congenital, familial and genetic disorders			
Pectus excavatum			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Asphyxiating thoracic dystrophy			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Cryptorchism			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
High arched palate			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Nervous system disorders			
Muscle contractions involuntary			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 22 (40.91%)		
occurrences (all)	11		
Teething			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Gastroesophageal reflux disease			

subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	8		
Abdominal distension			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Haematochezia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Dermatitis atopic			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Eczema			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dermatitis contact			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Dermatitis diaper			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	4		
Urticaria			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

Scoliosis subjects affected / exposed occurrences (all)	9 / 22 (40.91%) 12		
Deformity thorax subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Joint contracture subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Kyphosis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Torticollis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 22 (50.00%) 28		
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Otitis media subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 4		
Respiratory syncytial virus bronchiolitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3		
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Metabolism and nutrition disorders			

Feeding disorder subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 4		
Weight gain poor subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2017	Updated to include cardiac enzyme monitoring (CK-MB), added AVXS-101 dose determined through ddPCR with AveXis GMP product, and to require a total of 15 participants meeting the ITT criteria to be enrolled.
21 December 2017	Updated to clarify the data points which require review for the first three participants prior to continuing with enrollment. Additionally, a Day -1 CHOP-INTEND assessment was added.
04 October 2018	Updated to included updated and recent GLP toxicology data, to provide additional cardiac monitoring for patient safety, standardize infusion times within protocol, allow laboratory samples to be processed locally in certain instances, and to exclude participants from Bayley scales where English is not their first language to preserve the validity of the Bayley scales.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22467740