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	2017-000266-29
Trial protocol	GB FR SE BE ES NL IT
Global end of trial date	11 September 2020

Results information

Result version number	v2
This version publication date	10 April 2021
First version publication date	25 March 2021
Version creation reason	• Changes to summary attachments Changes needed to amendment section and dosage administration.

Trial information

Trial identification

Sponsor protocol code	AVXS-101-CL-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03461289
WHO universal trial number (UTN)	-
Other trial identifiers	Study Acronym: STR1VE-EU

Notes:

Sponsors

Sponsor organisation name	Novartis Gene Therapies, Inc
Sponsor organisation address	2275 Half Day Road , Bannockburn, IL , United States, 60015
Public contact	EMEA Medical Information, Novartis Gene Therapies EU Limited., +353 (1) 566-2364, medinfoemea.gtx@novartis.com
Scientific contact	EMEA Medical Information, Novartis Gene Therapies EU Limited., +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	11 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2020
Global end of trial reached?	Yes
Global end of trial date	11 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to determine efficacy by demonstrating achievement of developmental milestone of sitting without support for at least 10 seconds up to 18 months of age as assessed by World Health Organization (WHO) Motor Developmental Milestones.

Protection of trial subjects:

The trial was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and was consistent with ICH/GCP, applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2018
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	Belgium: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	33
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	33
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 33 participants took part in the trial in the United Kingdom, Italy, France and Belgium between August 2018 and September 2020.

Pre-assignment

Screening details:

Participants were screened up to 30 days before gene replacement therapy.

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	Onasemnogene abeparvovec-xioi

Arm description:

Participants received a single dose of onasemnogene abeparvovec-xioi administered as an intravenous (IV) infusion on Day 1 of the overall study.

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

Dosage and administration details:

Onasemnogene abeparvovec-xioi was administered via an IV infusion over 60 minutes at a dose of 1.1 × 10^14 vg/kg (vector genome per kilogram).

In order to dampen the host cellular immune response to the AAV-derived therapy, prophylactic prednisolone (or equivalent) was administered 24 hours before and for at least 30 days after dosing.

Number of subjects in period 1	Onasemnogene abeparvovec-xioi
Started	33
Completed	32
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	33	33	
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	4.055		
standard deviation	± 1.2799	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	14	14	

End points

End points reporting groups

Reporting group title	Onasemnogene abeparvovec-xioi

Reporting group description:

Participants received a single dose of onasemnogene abeparvovec-xioi administered as an intravenous (IV) infusion on Day 1 of the overall study.

Primary: Number of Participants Who Achieve Independent Sitting for at Least 10 Seconds

End point title	Number of Participants Who Achieve Independent Sitting for at Least 10 Seconds[1]

End point description:

Independent sitting is defined by the World Health Organization Multicentre Growth Reference Study, confirmed by video recording, as a participant who sits up straight with head erect for at least 10 seconds; participant does not use arms or hands to balance body or support position.

The analysis population was the Intent-to-Treat (ITT) population which consisted of symptomatic patients with bi-allelic deletion of SMN1 (exon 7/8 common homozygous deletions) and 2 copies of SMN2 without the known gene modifier mutation (c.859G>C) who received an IV infusion of Onasemnogene abeparvovec-xioi at less than 180 days of age.

End point type	Primary

End point timeframe:

From Study 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 analyses were planned for this endpoint.

End point values	Onasemnogene abeparvovec-xioi			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival at 14 Months of Age

End point title	Event-Free Survival at 14 Months of Age

End point description:

Event-free survival at 14 months of age was defined by avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, defined as requirement of tracheostomy or ≥16 hours of respiratory assistance per day (includes non-invasive ventilatory support) continuously for ≥14 days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

The observed proportion surviving in the AVXS-101-CL-302 study were compared to the natural history data of The Pediatric Neuromuscular Clinical Research (PNCR) network natural history study, using a 2-sided Fisher’s Exact test, along with the corresponding 95% confidence intervals.

End point type	Secondary

End point timeframe:

From Study Day 1 up to 14 Months of Age Visit

End point values	Onasemnogene abeparvovec-xioi			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Participants	31			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 30 days after the 18 months of age visit (up to a maximum of 17 months)

Adverse event reporting additional description:

Non-serious treatment emergent AEs were collected from Day 1 until 18 months of age visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Onasemnogene abeparvovec-xioi

Reporting group description:

Participants received a single dose of Onasemnogene abeparvovec-xioi administered as an intravenous (IV) infusion on Day 1 of the overall study.

Serious adverse events	Onasemnogene abeparvovec-xioi		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 33 (57.58%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coagulation test abnormal			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary function test			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hospitalisation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Loss of consciousness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Increased bronchial secretion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bronchiolitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Exanthema subitum			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Feeding disorder			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypernatraemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Onasemnogene abeparvovec-xioi		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 33 (96.97%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 33 (60.61%)		
occurrences (all)	29		
Crying			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Extravasation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Generalised oedema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypothermia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Necrosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	7		
Hypoxia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Lung consolidation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Respiratory disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Use of accessory respiratory muscles			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nervousness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Psychomotor retardation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Product issues			
Device occlusion			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	11		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	9		
Oxygen saturation decreased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Troponin T increased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Blood phosphorus decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Breath sounds			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Haemophilus test positive			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Platelet count increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory syncytial virus test positive			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Respirovirus test positive			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Staphylococcus test positive			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Contusion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Femur fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Hand fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Postoperative ileus			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Stoma site haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Stoma site inflammation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Vaccination complication			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Bradycardia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Cyanosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypersomnia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Ear and labyrinth disorders			

Tympanic membrane hyperaemia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Eye disorders Strabismus subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 15		
Constipation subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 7		
Diarrhoea subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 8		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
Teething subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Salivary hypersecretion subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Duodenal ulcer subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Gastritis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Oral pain			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	25		
Hepatic steatosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Acne infantile			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dermatitis atopic			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Excessive granulation tissue			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Ingrowing nail			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin reaction			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Muscle contracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	16		
Nasopharyngitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	8		
Respiratory tract infection			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Ear infection			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		

Candida infection				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Impetigo				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Pneumonia				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	3			
Urinary tract infection				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Bacteriuria				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	1			
Cystitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	1			
Dermatitis infected				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	1			
Fungal infection				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	2			
Gastroenteritis viral				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences (all)	1			

Hordeolum			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pharyngitis bacterial			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Roseola			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Failure to thrive			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Feeding disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hyperphosphatasaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2017	The following updates were made: • Addition of cardiac enzyme (CK-MB) monitoring • Added exclusion criterion for patients < 35 weeks gestational age at the time of birth • Updated Phase 1 study results added • Clarified wording related to autopsy and post-mortem tissue/organ collection • Updated until dose terminology based upon improved analytical method (ddPCR) with AveXis GMP product • Revised timepoints for laboratory assessments to allow for blood volume required for CK-MB monitoring • Added length of time for which mother should discontinue breastfeeding in instance of positive antibody titers. • Updated section on saliva, urine, and stool collection to reflect most recent viral shedding data • Minor clarifications and corrections were made to the overall document
09 January 2018	The following updates were made: • An administrative change to correct a discrepancy in capillary blood gas timepoint.
04 October 2018	The following updates were made: • Included recent Good Laboratory Practice (GLP) toxicology data • Added benefit/risk language from the Investigator Brochure • Updated onasemnogene abeparvovec-xioi infusion time to 60 minutes from 30-60 minutes. • Added language to allow for prednisolone equivalent • Deleted option for dilution of onasemnogene abeparvovec-xioi with normal saline • Updated schedule and timing of 12-Lead ECGs and echocardiograms • Added 24-hour Holter monitoring • Added Troponin I assessment • Updated immunology testing to remove ELISpot • Adjusted amount of blood volume required for laboratory assessments • Clarified collection of CK-MB and Troponin I relevant to enrollment • Added Pharmacovigilance reporting • Included an additional reference
17 May 2019	•Information on, and changes throughout the document as a result of, the acute liver failure case reported in the US Managed Access Program, including: - Update to the prophylactic administration of prednisolone regimen to dampen the immune response to AVXS 101 administration - Risk language updated to include description of recent adverse events and recommendations for liver safety, prolonged monitoring and detailed guidance on tapering of steroid use according to the language from the IB - Participant Exclusion Criterion 12 language updated to include more stringent criteria for liver function tests •Exploratory Objective and Exploratory Endpoint added to provide clarification on evaluation of independent sitting. •Participant Withdrawal Criteria updated to clarify that participants will be offered to continue on the long-term follow-up study. •Clarification provided regarding requirements for reporting elevated liver enzymes and reporting in the Clinical Trial Report. •To include Day 44 and Day 72 visits for blood chemistry, specifically LFTs

31 July 2019	•Removed exploratory objective and endpoint of ability to sit with support, in order to eliminate Bayley III item 19 which is not a defined milestone for this study •Clarified that 30 eligible participants were planned to be enrolled, but that patients who were already in screening at the time this enrollment target was met who met eligibility criteria could enroll upon approval of AveXis; this was so as to acknowledge that the number of participants may slightly exceed the enrollment target in this competitive enrolment trial •Added statement that patients who discontinue this trial prematurely will be invited to participate in the long-term follow up study •Updated description of the timing of post-treatment visits to be relative to date of gene therapy until the patient is 14 months of age (14 month of age visit), after which visits are to be relative to the patient's date of birth •Head circumference measurement was added to Physical Examination in order to align with the physical examination case report form •Removed statement that biological mothers who test positive for antibodies to AAV9 will be asked to refrain from breast feeding until at least 1 month after AVXS-101 dose
26 November 2019	The following updates were made: • Removal of Safety Objective to determine the safety of onasemnogene abeparvovec-xioi based on the development of unacceptable toxicity • Amended description of the role of the DSMB/DMC, timing and schedule of reviews, and recommendations and notification to regulatory authorities, as described in the DSMB/DMC Charter • Revised safety endpoints and analysis description • Risk language updated to include description of non-human primate (NHP) intrathecal study findings and the potential risk of neuronal toxicity following IT administration of onasemnogene abeparvovec-xioi • Detailed and age appropriate sensory testing added to be performed at each visit and any clinically significant abnormal finding recorded as an adverse event • Non-invasive ventilatory support usage recorded in the electronic Case Report Form (eCRF) to assist with identification of survival endpoints • All adverse events that occur after signing the informed consent through to the last trial visit collected and recorded in the eCRF • All SAEs (related and unrelated) recorded after signing of the consent form through 30 days after the last study visit • Trial enrolment not interrupted should any patient experience an unanticipated Grade 3 or higher related adverse event, pending DSMB/DMC review • Unanticipated Grade 3 or higher related adverse events will not be reported within 24 hours, unless they are adverse events of special interest (AESIs) or serious adverse events (SAEs) • AESIs, such as hepatotoxicity, thrombocytopenia, cardiac adverse events and sensory abnormalities potentially due to dorsal root ganglia inflammation are included/defined and the reporting requirements clarified • Elective procedures or minor surgeries where hospitalisation is required, should not be reported as SAE • Updated schedule of assessments and references.
25 June 2020	The following updates were made: • Insertion of new language to address the impact of COVID-19 on trial conduct • Key Contact Information and additional study contact information updated as part of administrative changes • Addition of abbreviations and definitions of terms • Application of consistent definition of primary endpoint and exploratory endpoints • Clarification of the collection and central review of videos of efficacy parameters • Insertion of specific safety reporting requirements of the French Competent Authority • Insertion of Hy's Law Criteria • Clarification and correction of statistical analysis definitions

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported