Sponsor

Novartis Gene Therapies, Inc (formerly AveXis Inc)

Generic Drug Name

AVXS-101 (onasemnogene abeparvovec-xioi)

Trial Indication(s)

Spinal Muscular Atrophy Type 1

Protocol Number

AVXS-101-CL-302 / COAV101A12301

Protocol Title

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

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

16 Aug 2018 to 11 Sep 2020

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) that enrolled 33 patients with spinal muscular atrophy (SMA) Type 1 who were genetically defined by a biallelic pathogenic mutation of the survival motor neuron gene (SMN1) with 1 or 2 copies of survival motor neuron 2 gene (SMN2).

The trial included a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provided informed consent, completed screening procedures to determine eligibility for study enrollment. Patients who met the entry criteria entered the in-patient gene replacement therapy period (Day -1 to Day 3).

On Day -1, patients were admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients received a one-time intravenous (IV) infusion of AVXS-101 and underwent inpatient safety monitoring over the next 48 hours. In order to dampen the host cellular immune response to the AAV-derived therapy, all patients received prophylactic prednisolone (or an equivalent dose of another glucocorticoid) from 2 days before till at least 1 month after the infusion followed by tapering. Variance from these recommendations was at the discretion of the Investigator based on potential safety issues for each patient. Patients could be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Trial at 18 months of age), patients returned at regularly scheduled intervals for efficacy and safety assessments until the End of Trial when the patient reached 18 months of age.

After the End of Trial visit, patients were invited to participate in a long-term follow up study conducted under a separate protocol, AVXS-101-LT-002.

Centers

The study was conducted in 10 centers in 4 European countries: Belgium (2), France (1), Italy (5), and the United Kingdom (2)

Objectives:

Primary objective(s)

The primary 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 defined by World Health Organization (WHO) Developmental Milestone.

Secondary objective(s)

The secondary objective was to determine efficacy based on survival at 14 months of age. Survival was defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation which was defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via noninvasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, was considered a surrogate for death.

Safety objective(s)

The safety objective was to evaluate the safety of AVXS-101 in patients with SMA Type 1.

Test Product (s), Dose(s), and Mode(s) of Administration

One time intravenous infusion of AVXS-101 over 60 minutes at a dose of 1.1 × 10^14 vg/kg (vector genome per kilogram).

Statistical Methods

Primary Efficacy: Sitting Without Support up to 18 months of age

The number and percent of patients whom, through video evidence, exhibited the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit was summarized for the intent-to-treat (ITT) population (and for identified subgroups). A one-sided Exact Binomial Test was used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 97.5% confidence intervals were estimated by the exact method for binomial proportions.

An additional set of sensitivity analyses was conducted to include patients who demonstrated the milestone of sitting without support, which occurred after but outside of the statistical analysis plan (SAP)-defined visit windows of the Month 18 of age visit due to COVID-19 disruptions.

Secondary Efficacy: Avoidance of Death or Surrogate for Death (Permanent Ventilation)

The proportion of patients surviving event-free to 14 months of age were assessed in the ITT population. Patients who terminated the study prior to reaching 14 months of age for any reason were considered treatment failures (event).

As a comparator, in a natural history study of SMA Type 1 patients, Finkel et al (2014), 16 patients reached the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days by 14 month of age, one patient discontinued the study at age of month 4 and 6 patients event-free survived at age of 14 months.

The observed proportion who survived in this study was compared to the natural history data of the matching cohort, using a 2-sided Fisher's Exact test, along with the corresponding 95% confidence intervals.

The number of patients survived in each subgroups were provided.

Time to death or permanent ventilation through 14 months of age was an additional sensitivity analysis. The survival rate at 14 months of age was estimated by Kaplan-Meier method, and survival curves for AVXS-101 treated patients and the Pediatric Neuromuscular Clinical Research Network (PNCR) cohort were compared using log-rank test at significance level of 0.05.

Additionally, the proportion of patients who experienced each of the following events by 14 months of age were summarized:

- Death
- Permanent ventilation

Safety Analysis

Safety was assessed through the incidence and severity of adverse events, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, immunology, urinalysis), physical examinations, and use of concomitant medications. Adverse events were coded in accordance with the Medical Dictionary of Regulatory Activities (MedDRA) coding

dictionary (Version 20.1 updated to Version 23.0). Prior and concomitant medications were coded in accordance with WHO DRUG (September 2017 updated to Global B3 March 2020).

Safety analyses was conducted on the safety population. The safety population consisted of all patients who received an IV infusion of AVXS-101.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients with SMA Type 1 as determined by diagnosis of SMA based on gene mutation analysis with biallelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2 [inclusive of the known SMN2 gene modifier mutation (c.859G>C)]
- Patients were eligible if < 6 months (< 180 days) of age at the time of AVXS-101 infusion
- Patients were required to have a swallowing evaluation test performed prior to administration of gene replacement therapy

Exclusion Criteria:

- Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age
- Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening
- Use or requirement of non-invasive ventilatory support for 12 or more hours daily in the two weeks prior to dosing
- Patients with signs of aspiration based on a swallowing test or whose weight-for-age falls below the 3rd percentile based on World Health Organization (WHO) Child Growth Standards and unwilling to use an alternative method to oral feeding
- Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (eg, nusinersen, valproic acid) at any time prior to screening for this trial.

Participant Flow Table (All Patients)

Disposition of Patients	Number (%) of Patients
Patients screened	41
Screen failures	8
Eligibility criteria not met	6 (75.0)
Withdrawal of consent/assent	1 (12.5)
Other	1 (12.5)
Patients in the All Enrolled population	33 (100)
Patients in the ITT population [1, 2]	32 (97.0)
Patients in the Safety population [1]	33 (100)
Patients in the Efficacy Completers population [1]	33 (100)
Patients in the Ability to Thrive ITT population [1]	23 (69.7)
Patients who completed the study [3]	32 (97.0)
Patients completed the study at <19 months of age [1]	26 (78.8)
Patients completed the study at ≥19 months of age [1]	6 (18.2)
Patients discontinued from the study [1]	1 (3.0)
Primary reason for discontinuation	
Death [1]	1 (3.0)

[1] Percentages are based on the number of patients in the All Enrolled Population
[2] One patient (024-003) was dosed at 181 days of age and hence excluded from ITT population.
[3] Completion of the study for an individual patient is defined as remaining in the study until the age of 18 months.

Baseline Characteristics (Safety Population)

Characteristic Category/Statistic	All Patients (N = 33)
Age at baseline (months) - continuous	
n	33
Mean (SD)	4.055 (1.2799)
Median (min, max)	4.100 (1.80, 6.00)
Age at baseline, n (%) – categorical	
In utero	0 (0.0)
Preterm newborn infants (gestational age < 37 wks)	0 (0.0)
Newborns (0-27 days)	0 (0.0)
Infants and toddlers (28 days-23 months)	33 (100.0)
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)
Sex, n (%)	
Male	14 (42.4)
Female	19 (57.6)
Weight at baseline (kg)	
n	33
Mean (SD)	5.839 (1.0386)
Median (Min, Max)	5.800 (4.20, 8.40)
Patients reported swallowing thin liquid n (%) [1]	
Yes	32 (97.0)
No	1 (3.0)
Reported feeding support, n (%)	
Yes	9 (27.3)

Characteristic Category/Statistic	All Patients (N = 33)
No	24 (72.7)
Reported ventilatory support, n (%) [2]	
Yes	9 (27.3)
No	24 (72.7)

[1] Defined as having a normal or functional swallow result for thin or very thin liquids during a formal swallow test.
[2] Based on the answer to the question “Does the patient require ventilatory support?” asked at the baseline pulmonary examination.

Primary Outcome Result(s)

Number of Patients Who Achieve Independent Sitting for at Least 10 Seconds at any Time up to 18 Months of Age Visit (ITT Population)

Time Frame: From Day 1 up to 18 months of age visit (up to a maximum of approximately 17 months)

Milestone	Statistics	AVXS-101 (N = 32)
Independent sitting for ≥ 10 seconds at any visit during the study	n (%)	14 (43.8)
	97.5% CI	(26.4, 100.0)
	p-value	<0.0001
Age when milestone was first demonstrated (months)[1]	n	14
	Mean (SD)	14.23 (4.340)
	Median (min, max)	15.90 (7.7, 18.6)

Note: A one-sided exact binomial test was used to test the null hypothesis of a p=0.1% at significance level of 0.025. The corresponding 97.5% confidence interval was estimated by the exact method for binomial proportions. Milestone is confirmed by independent central review.
[1] Due to COVID-19 pandemic situation, milestones achieved after day 570 are included.

Secondary Outcome Result(s)

Event-Free Survival at 14 Months of Age (ITT Population)

Time Frame: Up to 14 months of age

Statistics	AVXS-101 (N=32)
n (%)	31 (96.9)

Other Pre-specified Analysis

Number (%) of Participants surviving Event-Free to 14 months of Age (babies who were alive and did not need permanent ventilation at 14 months) vs. the data from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014

Time Frame: Up to 14 months of age

Statistics	AVXS-101 (N=32)	PNCR (N=23)
n (%)	31 (96.9)	6 (26.1)
95% CI[a]	(90.85, 100.00)	(8.14, 44.03)

Difference from PNCR (AVXS – PNCR)

Statistics	
Difference	0.71
SE Difference	0.10
95% CI[b]	0.48, 0.87
p-value	<0.0001

Note: Participants from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkle et al, 2014, were used as a historical control group for the open-label single-arm AVXS-101-CL-302 COAV101A12301 study.

Note: Note: Event-free survival at 14 months of age includes patients who did not die, did not require permanent ventilation and did not withdraw from the study by 14 months of age.
[a] Exact 95% confidence interval and corresponding p-value calculated from a two-sided Fisher's exact test with a significance level of 0.05 for the comparison between AVXS-101 and PNCR data.
[b] 95% Asymptotic Confidence Limits.

Safety Results

All-Cause Mortality (Safety population)

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

	Overall (N = 33) **n (%)**
Total participants affected	1 (3.0)

Serious Adverse Events and Deaths (Safety population)

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

	Overall (N = 33) **n (%)**
No. (%) of participants studied	33
No. (%) of participants with AE(s)	32 (97.0)
Number (%) of subjects with serious or other significant events	**Overall (N = 33)** **n (%)**
Death	1 (3.0)
SAE(s)	19 (57.6)
Discontinued due to SAE(s)	1 (3.0)

Serious Adverse Events by System Organ Class and Preferred Term (Safety population)

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

System Organ Class Preferred term	Overall (N = 33) n (%)
Participants with any treatment-emergent SAE	19 (57.6)
Blood and lymphatic system disorders	
Thrombocytopenia	1 (3.0)
Cardiac Disorders	
Bradycardia	1 (3.0)
Gastrointestinal disorders	
Dysphagia	1 (3.0)
Vomiting	1 (3.0)
General disorders	
Pyrexia	4 (12.1)
Hepatobiliary disorders	
Hypertransaminasaemia	1 (3.0)
Infections and infestations	
Bronchiolitis	2 (6.1)
Exanthema subitum	1 (3.0)
Gastroenteritis	3 (9.1)
Lower respiratory tract infection	2 (6.1)
Nasopharyngitis	1 (3.0)
Pneumonia	5 (15.2)
Respiratory syncytial virus infection	2 (6.1)
Respiratory tract infection	3 (9.1)
Rhinitis	1 (3.0)
Rhinovirus infection	1 (3.0)
Upper respiratory tract infection	3 (9.1)
Urinary tract infection	1 (3.0)
Viral infection	1 (3.0)

System Organ Class Preferred term	Overall (N = 33) n (%)
Investigations	
Alanine aminotransferase increased	1 (3.0)
Aspartate aminotransferase increased	1 (3.0)
Coagulation test abnormal	1 (3.0)
Pulmonary function test	1 (3.0)
Metabolism and nutrition disorders	
Feeding disorder	2 (6.1)
Hypernatraemia	1 (3.0)
Nervous System Disorders	
Hypoxic-ischaemic encephalopathy	1 (3.0)
Loss of consciousness	1 (3.0)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	1 (3.0)
Increased bronchial secretion	1 (3.0)
Respiratory distress	1 (3.0)
Respiratory failure	1 (3.0)
Surgical and medical procedures	
Gastrostomy	2 (6.1)
Hospitalisation	1 (3.0)

Non-Serious Adverse Events by System Organ Class (Safety population)

Time Frame: Day 1 until 18 months of age visit

System Organ Class Preferred term	Overall (N = 33) n (%)
Participants with any treatment-emergent non-SAE	32 (97.0)
Cardiac disorders	

System Organ Class Preferred term	Overall (N = 33) n (%)
Tachycardia	2 (6.1)
Bradycardia	1 (3.0)
Cyanosis	1 (3.0)
Congenital, familial and genetic disorders	
Cryptorchism	1 (3.0)
Ear and labyrinth disorders	
Tympanic membrane hyperaemia	1 (3.0)
Endocrine disorders	
Adrenal insufficiency	1 (3.0)
Eye disorders	
Strabismus	1 (3.0)
Gastrointestinal disorders	
Vomiting	8 (24.2)
Constipation	7 (21.2)
Diarrhoea	5 (15.2)
Gastrooesophageal reflux disease	4 (12.1)
Teething	3 (9.1)
Salivary hypersecretion	2 (6.1)
Abdominal pain	1 (3.0)
Duodenal ulcer	1 (3.0)
Gastritis	1 (3.0)
Oral pain	1 (3.0)
General disorders	
Pyrexia	20 (60.6)
Crying	1 (3.0)
Extravasation	1 (3.0)
Generalised oedema	1 (3.0)
Hypothermia	1 (3.0)
Necrosis	1 (3.0)
Hepatobiliary disorders	
Hypertransaminasaemia	8 (24.2)

System Organ Class Preferred term	Overall (N = 33) n (%)
Hepatic steatosis	1 (3.0)
Immune system disorders	
Drug hypersensitivity	1 (3.0)
Infections and infestations	
Upper respiratory tract infection	10 (30.3)
Nasopharyngitis	4 (12.1)
Respiratory tract infection	4 (12.1)
Ear infection	3 (9.1)
Gastroenteritis	3 (9.1)
Candida infection	2 (6.1)
Impetigo	2 (6.1)
Pneumonia	2 (6.1)
Rhinitis	2 (6.1)
Urinary tract infection	2 (6.1)
Bacteriuria	1 (3.0)
Bronchitis	1 (3.0)
Conjunctivitis	1 (3.0)
Cystitis	1 (3.0)
Dermatitis infected	1 (3.0)
Fungal infection	1 (3.0)
Gastroenteritis viral	1 (3.0)
Hordeolum	1 (3.0)
Influenza	1 (3.0)
Laryngitis	1 (3.0)
Lower respiratory tract infection	1 (3.0)
Otitis media	1 (3.0)
Pharyngitis bacterial	1 (3.0)
Respiratory tract infection viral	1 (3.0)
Roseola	1 (3.0)
Urinary tract infection bacterial	1 (3.0)
Varicella	1 (3.0)

System Organ Class Preferred term	Overall (N = 33) n (%)
Injury, poisoning and procedural complications	
Joint dislocation	3 (9.1)
Contusion	1 (3.0)
Femur fracture	1 (3.0)
Hand fracture	1 (3.0)
Postoperative ileus	1 (3.0)
Stoma site haemorrhage	1 (3.0)
Stoma site inflammation	1 (3.0)
Vaccination complication	1 (3.0)
Investigations	
Alanine aminotransferase increased	9 (27.3)
Aspartate aminotransferase increased	8 (24.2)
Oxygen saturation decreased	2 (6.1)
Troponin T increased	2 (6.1)
Blood alkaline phosphatase increased	1 (3.0)
Blood creatine phosphokinase MB increased	1 (3.0)
Blood phosphorus decreased	1 (3.0)
Blood urine present	1 (3.0)
Body temperature increased	1 (3.0)
Breath sounds	1 (3.0)
Gamma-glutamyltransferase increased	1 (3.0)
Haemoglobin decreased	1 (3.0)
Haemophilus test positive	1 (3.0)
Platelet count increased	1 (3.0)
Respiratory syncytial virus test positive	1 (3.0)
Respirovirus test positive	1 (3.0)
Staphylococcus test positive	1 (3.0)
Metabolism and nutrition disorders	
Decreased appetite	1 (3.0)
Failure to thrive	1 (3.0)
Feeding disorder	1 (3.0)

System Organ Class Preferred term	Overall (N = 33) n (%)
Hyperphosphatasaemia	1 (3.0)
Hypocalcaemia	1 (3.0)
Hypokalaemia	1 (3.0)
Hypomagnesaemia	1 (3.0)
Musculoskeletal and connective tissue disorders	
Scoliosis	2 (6.1)
Muscle contracture	1 (3.0)
Torticollis	1 (3.0)
Nervous system disorders	
Dizziness	1 (3.0)
Hypersomnia	1 (3.0)
Seizure	1 (3.0)
Product Issues	
Device occlusion	1 (3.0)
Psychiatric disorders	
Irritability	2 (6.1)
Nervousness	1 (3.0)
Psychomotor retardation	1 (3.0)
Renal and urinary disorders	
Leukocyturia	1 (3.0)
Respiratory, thoracic and mediastinal disorders	
Cough	6 (18.2)
Hypoxia	2 (6.1)
Dyspnoea	1 (3.0)
Lung consolidation	1 (3.0)
Nasal congestion	1 (3.0)
Respiratory disorder	1 (3.0)
Tachypnoea	1 (3.0)
Use of accessory respiratory muscles	1 (3.0)
Skin and subcutaneous tissue disorders	
Erythema	3 (9.1)

System Organ Class Preferred term	Overall (N = 33) n (%)
Rash	3 (9.1)
Acne infantile	1 (3.0)
Dermatitis allergic	1 (3.0)
Dermatitis atopic	1 (3.0)
Eczema	1 (3.0)
Excessive granulation tissue	1 (3.0)
Ingrowing nail	1 (3.0)
Skin reaction	1 (3.0)
Vascular disorders	
Hypertension	4 (12.1)
Hypotension	1 (3.0)

Other Relevant Findings

N/A

Conclusion:

The following conclusions can be made regarding the efficacy and safety of AVXS-101 based on observations made in this study:

- AVXS-101 treatment demonstrated statistically significant benefits in the primary endpoint of developmental milestone of sitting without support for ≥ 10 seconds at any visit up to and including the 18 months of age visit.
- AVXS-101 treatment demonstrated significantly marked improvement in the secondary endpoint of event-free survival at 14 months of age without permanent ventilation, compared to the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014.
- AVXS-101 was generally well tolerated in this patient population, and no new safety signals were identified in this study. Identified and potential risks for this investigational product are manageable in patients with SMA given the substantial efficacy associated with AVXS-101 treatment.

Date of Clinical Study Report:

6 May 2021