Sponsor

Novartis Gene Therapies, Inc.

Generic Drug Name

AVXS-101

Trial Indication(s)

Spinal Muscular Atrophy (SMA) Type 1

Protocol Number

AVXS-101-CL-101 / COAV101A12101

Protocol Title

Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

13-May-2014 to 14-Dec-2017

Reason for Termination

Not applicable

Study Design/Methodology

Study AVXS-101-CL-101 was a Phase 1, open-label, single-infusion, ascending-dose, single-center study to evaluate the safety and efficacy of AVXS-101 in up to 15 participants with Type 1 Spinal Muscular Atrophy (SMA).

When measured initially by a quantitative polymerase chain reaction (qPCR) assay, the Cohort 1 dose was assessed as 6.7 x 10^13 vector gram per kilogram (vg/kg) and the Cohort 2 dose was assessed as 2.0 x10^14 vg/kg. Subsequently the Cohort 2 dose was directly measured by a more developed and further validated Droplet Digital polymerase chain reaction (ddPCR) method to be 1.1 x 10^14 vg/kg. The intravenous dose of the AVXS-101 drug product manufactured by AveXis and used in all other studies is determined by the ddPCR assay and is 1.1 x 10^14 vg/kg.

AVXS-101 was injected intravenously through a peripheral limb vein. Short-term safety was evaluated over a two year period. Participants were tested at baseline and returned for follow-up visits on days 7, 14, 21, and 30, and were followed once every month through 12 months post-infusion, and then every 3 months through 2 years post-infusion. Unscheduled visits occurred if the principal investigator (PI) determined that they were necessary.

15 participants were enrolled, 3 in cohort 1 and 12 in cohort 2.

Centers

1 center in the United States

Objectives:

Primary objective(s)

The primary objective of the study was safety.

Secondary objective(s)

Efficacy objectives were secondary objectives. The primary efficacy endpoint was the time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes bi-level positive airway pressure [BiPAP]) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death.

Other secondary objectives included:

- The change from baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score
- demonstration of improvement of motor function and muscle strength as determined by achievement of functional independent sitting.

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

For the 3 participants in cohort 1, 6.7 X 10^13 vg/kg (as measured by qPCR) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein. For the 12 participants in Cohort 2, 2.0 X 10^14 vg/kg (as measured by qPCR) of AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein. Subsequently the Cohort 2 dose was determined to be 1.1 x 10^14 vg/kg using a more developed and fully validated ddPCR method.

Statistical Methods

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

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 (AEs) were coded in accordance with the Medical Dictionary of Regulatory Activities (MedDRA)

coding dictionary (Version 20.0). Prior and concomitant medications were coded in accordance with World Health Organization (WHO) DRUG (Dictionary B2 Enhanced 2017).

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

Efficacy: Number of Participants Who Experienced Permanent Ventilation or Death

The proportion of participants surviving event-free to each efficacy data cutoff was computed for each cohort in the intent-to-treat (ITT population). The primary efficacy cutoff occurred when the last participant reached 13.6 months of age. Participants who terminated the study for any reason before the efficacy data cutoff were considered having met the endpoint. As a comparator, in a natural history study of SMA Type 1 participants, it was estimated that only 25% of SMA Type 1 participants with 2 copies of survival of motor neuron 2 (SMN2) would survive event-free to 13.6 months of age. The observed proportion of participants surviving in the current study at the primary efficacy data cutoff was compared to the natural history estimate of 25% using a 1-sample exact binomial test. This comparison was performed separately for each cohort.

Efficacy: Mean Change from Baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) Score

The change from baseline in CHOP-INTEND score was analyzed by using mixed model repeated measures (MMRM). The model for the full analysis set (FAS) included the change from baseline as the dependent variable, and fixed effects of cohort, visit, and a covariate of baseline, and interactions of cohort-visit, baseline-visit.

Efficacy : Number of Participants Achieving Functional Independent Sitting

External expert confirmation of milestone achievements captured during physical therapy assessments on video recordings is considered the principal reference for milestone attainment data. The number (%) of participants who exhibited evidence of milestone achievement by the time of each efficacy data analysis time point was summarized by cohort using the FAS. The observed proportion attaining these milestones was compared to the expected rate of attainment among untreated participants with SMA Type 1 (zero) using a 1-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% was used in place of literal zero.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

Six or nine months of age and younger (depending on cohort) on day of vector infusion with Type 1 SMA as defined by the following features:

- Diagnosis of SMA based on gene mutation analysis with bi-allelic survival of motor neuron 1 (SMN1) mutations (deletion or point mutations) and 2 copies of SMN2.
- Onset of disease at birth up to 6 months of age.
- Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints.

Exclusion Criteria:

- Active viral infection (includes human immunodeficiency virus [HIV] or serology positive for hepatitis B or C)
- Use of invasive ventilatory support (tracheotomy with positive pressure)* or pulse oximetry <95% saturation.
- Participants may be put on non-invasive ventilator support (BiPAP) for less than 16 hours a day at the discretion of their physician or research staff.
- Concomitant illness that in the opinion of the Principal Investigator (PI) creates unnecessary risks for gene transfer
- Concomitant use of any of the following drugs: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab)
- Participants with Anti-AAV9 antibody titers >1:50 as determined by enzyme-linked immunosorbent assay (ELISA) binding immunoassay.
- Abnormal laboratory values considered clinically significant (gamma-glutamyl transferase [GGT] > 3X upper limit of normal [ULN], bilirubin ≥ 3.0 milligram/deciliter [mg/dL] , creatinine ≥ 1.8 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/Dl; white blood cells [WBC] > 20,000 per cubic meters per minute [cmm]) Participation in a recent SMA treatment clinical trial that in the opinion of the PI creates unnecessary risks for gene transfer.

- Family does not want to disclose participant's study participation with primary care physician and other medical providers.
- Participant with signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding.
- Participants with a single base substitution in SMN2 (c.859G>C in exon 7) will be excluded based on predicted mild phenotype.

Participant Flow Table (All Participants)

Summary of Participant Disposition at 24 Months Post-Dose and Analysis Sets (All Participants)

	Number of Participants		
	Cohort 1 N = 3 n (%)	Cohort 2 N = 12 n (%)	All Participants N = 15 n (%)
Disposition of Participants			
Received AVXS-101 infusion	3 (100)	12 (100)	15 (100)
Completed the study at 24 months of follow-up	3 (100)	12 (100)	15 (100)
Discontinued study before primary efficacy data cut off	0 (0)	0 (0)	0 (0)
Discontinued study before 24 months of follow-up	0 (0)	0 (0)	0 (0)
Analysis Sets			
Safety analysis set[a]	3 (100)	12 (100)	15 (100)
ITT analysis set[a]	3 (100)	12 (100)	15 (100)

ITT
a Safety and ITT analysis sets included any participants who underwent gene therapy infusion.

Baseline Characteristics (Safety Analysis Set)

Summary of Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic Category/Statistic	Cohort 1 (N = 3) n (%)	Cohort 2 (N = 12) n (%)	All Participants (N = 15) n (%)
Age at Day 0[a] (months)			
Mean (SD)	6.3 (0.75)	3.4 (2.06)	4.0 (2.21)
Median	5.9	3.1	4.1
Min, Max	5.9, 7.2	0.9, 7.9	0.9, 7.9
Sex, n (%)			
Male	1 (33.3)	5 (41.7)	6 (40.0)
Female	2 (66.7)	7 (58.3)	9 (60.0)
Race, n (%)			
White	3 (100)	11 (91.7)	14 (93.3)
Other	0 (0)	1 (8.3)	1 (6.7)
Ethnicity, n (%)			
Not Hispanic or Latino	3 (100)	10 (83.3)	13 (86.7)
Hispanic or Latino	0 (0)	2 (16.7)	2 (13.3)
Region of Enrollment, n (%)			
United States	3 (100)	12 (100)	15 (100)
SMN2 Copy Number = 2			
Number of participants	3 (100)	12 (100)	15 (100)
Bi-allelic Deletions of SMN1			
Number of participants	3 (100)	12 (100)	15 (100)
Exon 7 Gene Modifier Mutation			
Number of participants	0 (0)	0 (0)	0 (0)

SD = standard deviation; Max = maximum; Min = minimum; SMA = spinal muscular atrophy.

[a] Day of AVXS-101 administration.

[b] Does not include one additional participant in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site (AveXis data on file).

Primary Outcome Result(s)

Number of Participants Who Experienced a Treatment-related Unacceptable Toxicity (Safety Population)

Time frame: Up to 24 months post-dose

Statistics	Cohort 1 (N=3) Units: Participants	Cohort 2 (N=12) Units: Participants
n (%)	1 (33.3)	3 (25.0)

Secondary Outcome Result(s)

Number of Participants Who Experienced Permanent Ventilation or Death at 13.6 Months of Age (ITT Population)

Time frame: Up to 13.6 months of age

Statistics	Cohort 1 (N=3) Units: Participants	Cohort 2 (N=12) Units: Participants
n (%)	0 (0.00)	0 (0.00)

Change from Baseline in Mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) Score (Full Analysis Set)

Time frame: Baseline to 24 months post-dose

Month	Cohort 1 (N=0) Mean (Standard Deviation) Units: Percentage Change	Cohort 2 (N=6) Mean (Standard Deviation) Units: Percentage Change
Mean (±Standard Deviation)	NA	30.7 ± 145.61

CHOP-INTEND assessments were discontinued once patients achieved higher functioning status, so the number of available data points decreased over time.

Number of Participants Achieving Functional Independent Sitting for at Least 30 Seconds (Full Analysis Set)

Time frame: Up to 24 months post-dose

Full analysis set (N = 15)	n (%)	2-sided 95.0% CI[a] (%)	p-value[a]
Cohort 1 (N = 3)	0	0.00, 70.76	1.000
Cohort 2 (N = 12)	9 (75.0)	42.81, 94.51	<0.001
All patients (N = 15)	9 (60.0)	32.29, 83.66	<0.001

CI = confidence interval;
Note: Cohort 1 received low dose AVXS-101 (6.7E13 vg/kg) and Cohort 2 received intermediate dose of AVXS-101 (2.0E14 vg/kg).
a Observed percent compared to zero using a one-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% will be used in place of a literal zero.

Other Pre-specified Analysis

Number of Participants Achieving Functional Independent Sitting for at Least 30 Seconds (Full Analysis Set)

Time frame: Up to 24 months post-dose

Full analysis set (N = 15)	n (%)	2-sided 95.0% CI[a] (%)	p-value[a]
Cohort 1 (N = 3)	0	0.00, 70.76	1.000
Cohort 2 (N = 12)	9 (75.0)	42.81, 94.51	<0.001
All patients (N = 15)	9 (60.0)	32.29, 83.66	<0.001

CI = confidence interval;
Note: Cohort 1 received low dose AVXS-101 (6.7E13 vg/kg) and Cohort 2 received intermediate dose of AVXS-101 (2.0E14 vg/kg).
a Observed percent compared to zero using a one-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% will be used in place of a literal zero.

Statistical Analysis	
Comments	Data for the current study were compared to historical control data (Pediatric Neuromuscular Clinical Research [PNCR], Finkel et al 2014 - PubMed 25080519) where 0 participants were able to sit independently.
Type of Statistical Test	Superiority
P-Value	<0.001
Method	One-sided Exact Binomial Test

Safety Results

Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

Time frame: Adverse events were collected from the single dose of study treatment until 24 months post dose.

	Number (%) of Participants		
	Cohort 1 N = 3	Cohort 2 N = 12	All Participants N = 15
Any TEAE	3 (100)	12 (100)	15 (100)
TEAEs possibly related to AVXS-101[a]	0	0	0
TEAEs probably related to AVXS-101[a]	0	0	0
TEAEs definitely related to AVXS-101[a]	1 (33.3)	3 (25.0)	4 (26.7)
Severe TEAE	3 (100)	10 (83.3)	13 (86.7)
Serious TEAE	3 (100)	10 (83.3)	13 (86.7)
TEAE leading to study discontinuation	0	0	0
Fatal TEAE	0	0	0
Number of deaths[b]	0	0	0

TEAE = treatment-emergent adverse event.
Note: Cohort 1 received low dose AVXS-101 (6.7E13 vg/kg) and Cohort 2 received intermediate dose of AVXS-101 (2.0E14 vg/kg).
a As assessed by the investigator.

b Includes non-TEAE deaths.

Serious Adverse Events and Deaths

Summary of Serious Treatment-emergent Adverse Events (Safety Analysis Set)

Time frame: Adverse events were collected from the single dose of study treatment until 24 months post dose.

System Organ Class Preferred Term	Number (%) of Participants		
	Cohort 1 (N = 3)	Cohort 2 (N = 12)	All Participants (N = 15)
Any serious TEAE	3 (100)	10 (83.3)	13 (86.7)
Cardiac disorders			
Tachycardia	0	1 (8.3)	1 (6.7)
Infections and infestations			
Pneumonia	0	7 (58.3)	7 (46.7)
Parainfluenzae virus infection	1 (33.3)	2 (16.7)	3 (20.0)
Pneumonia respiratory syncytial viral	1 (33.3)	2 (16.7)	3 (20.0)
Respiratory syncytial virus bronchiolitis	1 (33.3)	2 (16.7)	3 (20.0)
Upper respiratory tract infection	0	3 (25.0)	3 (20.0)
Adenovirus infection	0	2 (16.7)	2 (13.3)
Enterovirus infection	0	2 (16.7)	2 (13.3)
Rhinovirus infection	0	2 (16.7)	2 (13.3)
Bronchitis	1 (33.3)	0	1 (6.7)
Gastroenteritis	0	1 (8.3)	1 (6.7)
Gastroenteritis viral	0	1 (8.3)	1 (6.7)
Influenza	1 (33.3)	0	1 (6.7)
Lower respiratory tract infection	0	1 (8.3)	1 (6.7)
Pneumonia parainfluenzae viral	0	1 (8.3)	1 (6.7)
Pneumonia viral	0	1 (8.3)	1 (6.7)
Postoperative wound infection	0	1 (8.3)	1 (6.7)

Viral upper respiratory tract infection	0	1 (8.3)	1 (6.7)
Injury, poisoning and procedural complications			
Femur fracture	0	1 (8.3)	1 (6.7)
Post procedural haemorrhage	0	1 (8.3)	1 (6.7)
Investigations			
Human rhinovirus test positive	0	2 (16.7)	2 (13.3)
Transaminases increased	1 (33.3)	1 (8.3)	2 (13.3)
Enterovirus test positive	0	1 (8.3)	1 (6.7)
Norovirus test positive	0	1 (8.3)	1 (6.7)
Oxygen saturation decreased	0	1 (8.3)	1 (6.7)
Metabolism and nutrition disorders			
Dehydration	0	1 (8.3)	1 (6.7)
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration	0	2 (16.7)	2 (13.3)
Respiratory distress	0	2 (16.7)	2 (13.3)
Atelectasis	0	1 (8.3)	1 (6.7)
Respiratory failure	1 (33.3)	0	1 (6.7)

Treatment-emergent SAEs were defined as events with an onset date on or after the date of AVXS-101 infusion through 30 days after the last study visit. At each level of summation (SOC, PT) participants reporting more than 1 SAE are counted only once.

Other (Non-serious) Treatment-emergent Adverse Events by Preferred Term n (%) (0% Threshold) (Safety Analysis Set)
Time frame: Adverse events were collected from the single dose of study treatment until 24 months post dose.

System Organ Class Preferred Term	Number (%) of Participants		
	Cohort 1 (N = 3)	Cohort 2 (N = 12)	All Participants (N = 15)
Total subjects affected by non-serious adverse events	3 (100.0)	12 (100.0)	15 (100)
Vascular disorders			
Hypertension	0	1 (8.3)	1 (6.7)
Immune system disorders			0 (0)
Food allergy	0	1 (8.3)	1 (6.7)
Hypersensitivity	0	1 (8.3)	1 (6.7)
General disorders and administration site conditions			
Catheter site dermatitis	1 (33.3)	0	1 (6.7)
Catheter site inflammation	1 (33.3)	0	1 (6.7)
Catheter site pain	0	1 (8.3)	1 (6.7)
Pain	0	1 (8.3)	1 (6.7)
Pyrexia	1 (33.3)	7 (58.3)	8 (53.3)
Secretion discharge	0	1 (8.3)	1 (6.7)
Injury, poisoning and procedural complications			
Fall	0	3 (25.0)	3 (20.0)
Femur fracture	0	1 (8.3)	1 (6.7)
Humerus fracture	1 (33.3)	0	1 (6.7)
Lower limb fracture	1 (33.3)	0	1 (6.7)
Mouth injury	0	1 (8.3)	1 (6.7)

Procedural pain	0	1 (8.3)	1 (6.7)
Tibia fracture	0	1 (8.3)	1 (6.7)
Traumatic haematoma	0	1 (8.3)	1 (6.7)
Wound	0	1 (8.3)	1 (6.7)
Investigations			
Aspartate aminotransferase increased	0	1 (8.3)	1 (6.7)
Enterovirus test positive	0	1 (8.3)	1 (6.7)
Eosinophil count increased	0	1 (8.3)	1 (6.7)
Haemoglobin decreased	0	1 (8.3)	1 (6.7)
Human rhinovirus test positive	0	2 (16.7)	2 (13.3)
Transaminases increased	0	2 (16.7)	2 (13.3)
Cardiac disorders			
Bradycardia	0	1 (8.3)	1 (6.7)
Tachycardia	0	1 (8.3)	1 (6.7)
Ventricular hypertrophy	0	1 (8.3)	1 (6.7)
Blood and lymphatic system disorders			
Anaemia	0	1 (8.3)	1 (6.7)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	0	1 (8.3)	1 (6.7)
Aspiration	0	1 (8.3)	1 (6.7)
Atelectasis	0	3 (25.0)	3 (20.0)
Cough	0	5 (41.7)	5 (33.3)
Dyspnoea	0	1 (8.3)	1 (6.7)
Epistaxis	0	1 (8.3)	1 (6.7)
Hypoxia	0	1 (8.3)	1 (6.7)

Nasal congestion	0	6 (50.0)	6 (40.0)
Nasal oedema	1 (33.3)	0	1 (6.7)
Pleural effusion	1 (33.3)	0	1 (6.7)
Respiratory failure	0	3 (25.0)	3 (20.0)
Respiratory tract congestion	0	1 (8.3)	1 (6.7)
Rhinitis allergic	0	1 (8.3)	1 (6.7)
Rhinorrhoea	0	3 (25.0)	3 (20.0)
Snoring	0	1 (8.3)	1 (6.7)
Tachypnoea	0	1 (8.3)	1 (6.7)
Upper respiratory tract congestion	1 (33.3)	0	1 (6.7)
Wheezing	0	2 (16.7)	2 (13.3)
Eye disorders			
Blepharitis	0	1 (8.3)	1 (6.7)
Chalazion	1 (33.3)	0	1 (6.7)
Dry eye	0	1 (8.3)	1 (6.7)
Gastrointestinal disorders			
Abdominal distension	0	1 (8.3)	1 (6.7)
Abdominal pain	0	1 (8.3)	1 (6.7)
Constipation	1 (33.3)	6 (50.0)	7 (46.7)
Diarrhoea	0	3 (25.0)	3 (20.0)
Dysphagia	0	1 (8.3)	1 (6.7)
Gastric hypomotility	1 (33.3)	0	1 (6.7)
Gastrooesophageal reflux disease	1 (33.3)	5 (41.7)	6 (40.0)
Haematemesis	0	1 (8.3)	1 (6.7)
Haematochezia	0	1 (8.3)	1 (6.7)

Hiatus hernia	0	1 (8.3)	1 (6.7)
Nausea	0	1 (8.3)	1 (6.7)
Teething	1 (33.3)	0	1 (6.7)
Vomiting	0	8 (66.7)	8 (53.3)
Skin and subcutaneous tissue disorders			
Acne infantile	0	1 (8.3)	1 (6.7)
Alopecia	0	1 (8.3)	1 (6.7)
Decubitus ulcer	0	2 (16.7)	2 (13.3)
Dermatitis allergic	0	1 (8.3)	1 (6.7)
Eczema	0	1 (8.3)	1 (6.7)
Erythema	1 (33.3)	1 (8.3)	2 (13.3)
Excessive granulation tissue	1 (33.3)	0	1 (6.7)
Rash	0	5 (41.7)	5 (33.3)
Rash generalised	0	1 (8.3)	1 (6.7)
Skin discolouration	0	1 (8.3)	1 (6.7)
Urticaria	1 (33.3)	0	1 (6.7)
Musculoskeletal and connective tissue disorders			
Mastication disorder	0	1 (8.3)	1 (6.7)
Muscular weakness	0	1 (8.3)	1 (6.7)
Osteopenia	0	1 (8.3)	1 (6.7)
Scoliosis	0	1 (8.3)	1 (6.7)
Metabolism and nutrition disorders			
Dehydration	0	1 (8.3)	1 (6.7)
Fluid overload	0	1 (8.3)	1 (6.7)
Hyperglycaemia	1 (33.3)	0	1 (6.7)

Hypoglycaemia	0	1 (8.3)	1 (6.7)
Infections and infestations			
Alpha haemolytic streptococcal infection	0	1 (8.3)	1 (6.7)
Bronchiolitis	0	3 (25.0)	3 (20.0)
Catheter site cellulitis	1 (33.3)	0	1 (6.7)
Clostridium difficile colitis	0	1 (8.3)	1 (6.7)
Conjunctivitis	0	2 (16.7)	2 (13.3)
Ear infection	1 (33.3)	2 (16.7)	3 (20.0)
Enterovirus infection	0	4 (33.3)	4 (26.7)
Gastroenteritis viral	0	4 (33.3)	4 (26.7)
Influenza	0	1 (8.3)	1 (6.7)
Lower respiratory tract infection	0	1 (8.3)	1 (6.7)
Metapneumovirus infection	0	1 (8.3)	1 (6.7)
Oral candidiasis	0	1 (8.3)	1 (6.7)
Otitis externa	0	1 (8.3)	1 (6.7)
Otitis media	2 (66.7)	2 (16.7)	4 (26.7)
Otitis media acute	0	1 (8.3)	1 (6.7)
Parainfluenzae virus infection	0	2 (16.7)	2 (13.3)
Pharyngitis	0	1 (8.3)	1 (6.7)
Pharyngitis streptococcal	1 (33.3)	2 (16.7)	3 (20.0)
Pneumonia	0	4 (33.3)	4 (26.7)
Pneumonia viral	0	1 (8.3)	1 (6.7)
Pseudomonas infection	1 (33.3)	0	1 (6.7)
Respiratory tract infection	0	1 (8.3)	1 (6.7)
Rhinovirus infection	1 (33.3)	4 (33.3)	5 (33.3)

Staphylococcal bacteraemia	0	1 (8.3)	1 (6.7)
Staphylococcal infection	1 (33.3)	0	1 (6.7)
Tonsillitis	1 (33.3)	0	1 (6.7)
Upper respiratory tract infection	1 (33.3)	10 (83.3)	11 (73.3)
Urinary tract infection	0	2 (16.7)	2 (13.3)
Viral infection	0	1 (8.3)	1 (6.7)
Viral upper respiratory tract infection	0	2 (16.7)	2 (13.3)
Wound infection	0	1 (8.3)	1 (6.7)

Other Relevant Findings

N/A

Conclusion:

AVXS-101 demonstrated an acceptable safety profile.

Treatment with AVXS-101 demonstrated remarkable efficacy during the course of this study. The main efficacy analyses were conducted when all patients reached at least 13.6 months of age. The primary efficacy endpoint was survival, defined as time from birth date to either (a) death or (b) permanent ventilation. All 12 patients (100%) in Cohort 2 survived without permanent ventilation, a rate significantly higher than the 25% natural history survival rate, as observed in the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), and reported by Finkel et al, 2014, for the 13.6 months of age time point.

Participants in Cohort 2 achieved statistically significant and clinically meaningful improvements in the critical motor milestones of early development of independent sitting for ≥ 30 seconds. At the end of the 24-month post-infusion follow-up period, 9 participants in Cohort 2 (75.0%) were able to sit for ≥30 seconds without assistance, an achievement not reported in participants with SMA Type 1, per the natural history PNCR database reported by Finkel et al, 2014.

Event-free survival persisted throughout the study for Cohort 2 patients through until the end-of-study 24-month post-dose follow-up visit.

Date of Clinical Study Report

14 August 2018