NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Gene Therapies

Generic Drug Name

AVXS-101 (onasemnogene abeparvovec-xioi)

Trial Indication(s)

Spinal Muscular Atrophy Type 1

Protocol Number

AVXS-101-CL-303 / COAV101A12302

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 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: October 2017 (Actual)
Primary Completion Date: November 2019 (Actual)

Study Completion Date: November 2019 (Actual)

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 up to 20 patients (planned) with Spinal Muscular Atrophy (SMA) Type 1 who were either symptomatic or pre-symptomatic with no functional survival motor neuron (*SMN)1* gene as 1 or 2 copies of *SMN2* and who were < 6 months (< 180 days) of age at the time of gene therapy (Day 1).

The study included 3 study periods: screening, gene replacement therapy, and follow-up. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent did undergo screening procedures to determine eligibility for study enrollment. Patients who met the entry criteria entered the inpatient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients were admitted to the hospital for pretreatment baseline procedures. On Day 1, patients received a one-time intravenous (IV) infusion of AVXS-101 at a dose equivalent to the dose received by the second dosing Cohort in the Phase 1 study over approximately 30-60 minutes and underwent inpatient safety monitoring over the next 48 hours. Patients were discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients returned at regularly scheduled intervals for efficacy and safety assessments until the patient reached 18 months of age.

All post-treatment visits were relative to the date on which gene replacement therapy was administered, except for the 14 and 18 months of age visits, which were relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient returned within 0 to 14 days after the date on which the patient reached 14 and 18 months of age, respectively. The 18 months of age visit also served as the End of Study visit. After the End of Study visit, eligible patients were asked to enroll into the long-term follow-up study.

Twenty two patients were enrolled.

Centers

United States(16)

Objectives:

Primary: The co-primary objectives were to:

1. Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
2. Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

Secondary: The co-secondary objectives were to:

1. Determine the effect of AVXS-101 on the ability to thrive, defined as achieving all of the following at 18 months of age
    a. Did not receive nutrition through mechanical support or other non-oral method (e.g., feeding tube)
    b. Ability to tolerate thin liquids as demonstrated through a formal swallowing test
    c. Maintained weight (> third percentile for age and gender)
2. Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device, for patients issued a Trilogy 100 Bi-level Positive Airway Pressure (BiPAP) device

Safety: The safety objectives were to:

1. Evaluate the safety of AVXS-101 in patients with spinal muscular atrophy (SMA) Type 1
2. Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, unanticipated, treatment-related toxicity.

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

One time intravenous infusion of AVXS-101 at a dose of 1.1E14 vg/kg.

Statistical Methods

Safety

Safety was assessed based on all patients who underwent gene therapy at Day 1. The primary population for the primary and secondary efficacy analyses was the ITT population. Patients with 1 copy of *SMN2*, pre-symptomatic patients, and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the Intent-to-Treat (ITT) population were evaluated separately as part of additional subgroup analyses.

Safety was assessed through the incidence and severity of adverse events (AEs), vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, urinalysis, and immunology), 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).

Safety analyses were conducted on safety population and summarized by subgroup and overall.

Efficacy

This study compared the activity of AVXS 101 administered intravenously versus the natural observational results from Pediatric Neuromuscular Clinical Research Network (PNCR) in terms of functional independent sitting and survival rate. The ability to thrive and the ability to remain independent of ventilatory support were also assessed.

The analysis of the co-primary and co-secondary efficacy endpoints were performed for the ITT and efficacy completer's population. The analysis based on the ITT population was considered as the primary analysis. In the case of missing data, observed data were used for the analyses.

Unless otherwise specified, the baseline measurement was defined as the last non-missing measurement collected prior to or on the day of gene replacement therapy infusion (e.g., on or before Day 1 visit).

Functional independent sitting and the 2 co-secondary endpoints were assessed with 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. 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.

Event-free survival was assessed with a 2 sample 2-sided Fischer's exact test was used to test the null hypothesis of p=historical at the significance level of 0.05. Participant-level data was drawn from the PNCR study with 25% participants surviving at 13.6 months.

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. Similarly, 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.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Participants with SMA Type 1 as determined by the following features: a. Diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 1 or 2 copies of SMN2 (inclusive of the known SMN2 gene modifier mutation (c.859G>C))2
• The first 3 participants enrolled must meet the criteria for the Intent-To-Treat Population
• Participants must be < 6 months (< 180 days) of age at the time of onasemnogene abeparvovec-xioi infusion
• Participants must have a swallowing evaluation test performed prior to administration of gene replacement therapy
• Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics
• Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

Exclusion Criteria:

• Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
• Pulse oximetry < 96% saturation at screening while the participant is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease

by ≥ 4 percentage points
• Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
• Participants with signs of aspiration/inability to tolerate non-thickened- liquids based on a formal swallowing test performed as part of screening. Participants with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study
• Participants whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards
• Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
• Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
• Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
• Severe non-pulmonary/respiratory tract infection within 4 weeks before administration of gene replacement therapy or concomitant illness that creates unnecessary risks for gene replacement therapy such as: a. Major renal or hepatic impairment b. Known seizure disorder c. Diabetes mellitus d. Idiopathic hypocalcuria e. Symptomatic cardiomyopathy
• Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
• Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy
• Anti-adeno-associated virus serotype 9 (AAV9) antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential participant demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
• Clinically significant abnormal laboratory values (gamma glutamyl- transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy
• Participation in recent SMA treatment clinical study (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 at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
• Expectation of major surgical procedures during the study assessment period
• Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
• Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites

- Parent(s)/legal guardian(s) refuses to sign consent form
- Gestational age at birth < 35 weeks (245 days)

Participant Flow Table

Overall Study

	Onasemnogene Abeparvovec-xioi	Total
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote	

	intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.	
Started	22	22
Completed	19	19
Not Completed	3	3
Death	1	1
Adverse Event	1	1
Withdrawal by Subject	1	1

Baseline Characteristics

	Onasemnogene Abeparvovec-xioi	**Total**
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated	

	virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.	
Number of Participants [units: participants]	22	22
Age Categorical (units: participants) Count of Participants (Not Applicable)		
<=18 years	22	
Between 18 and 65 years	0	
>=65 years	0	
Age Continuous (units: months) Mean ± Standard Deviation		

	3.7±1.6
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)	
Female	12
Male	10
Ethnicity (NIH/OMB) (units: participants) Count of Participants (Not Applicable)	
Hispanic or Latino	4
Not Hispanic or Latino	18
Unknown or Not Reported	0
Race (NIH/OMB) (units: participants) Count of Participants (Not Applicable)	
American Indian or Alaska Native	0
Asian	2
Native Hawaiian or Other Pacific Islander	0
Black or African American	3
White	11
More than one race	0
Unknown or Not Reported	6
Region of Enrollment (units: participants)	
United States	22

Patient reported hospitalizations (units: participants)	
Yes	17
No	5
Weight at baseline (units: kg) Mean ± Standard Deviation	
	5.8±1.1
Height/length at baseline (units: cm) Mean ± Standard Deviation	
	61.3±4.3

Primary Outcome Result(s)

Achievement of independent sitting for at least 30 seconds

(Time Frame: Up to 18 months)

	Onasemnogene Abeparvovec-xioi
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant

	adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Number of Participants Analyzed [units: participants]	22
Achievement of independent sitting for at least 30 seconds (units:) Count of Participants (Not Applicable)	
	13 (59.09%)

Statistical Analysis

Groups	Onasemnogene Abeparvovec-xioi	This comparison is made to an assumed rate of zero 0 (or as low as 0.1%). By definition, children with spinal muscular atrophy Type 1 are never able to sit independently.
P Value	<0.0001	
Method	Other One-sided Exact Binomial Test	

Event-free survival

(Time Frame: 14 months)

	Onasemnogene Abeparvovec-xioi
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV)

	enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Number of Participants Analyzed [units: participants]	22
Event-free survival (units:) Count of Participants (Not Applicable)	
	20 (90.91%)

Secondary Outcome Result(s)

Ability to thrive

(Time Frame: 18 months)

	Onasemnogene Abeparvovec-xioi
Arm/Group Description	One-time Intravenous administration of

	onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Number of Participants Analyzed [units: participants]	22
Ability to thrive (units:)	

Count of Participants (Not Applicable)	
	9 (40.91%)

Ventilatory support independence

(Time Frame: Up to 18 months)

	Onasemnogene Abeparvovec-xioi
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to

	promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Number of Participants Analyzed [units: participants]	22
Ventilatory support independence (units:) Count of Participants (Not Applicable)	
	18 (81.82%)

Other Pre-specified Analysis

Event-free survival - as compared to the Pediatric Neuromuscular Clinical Research (PNCR) natural history data sets [Neurol. 2014; 83(9):810-817]

(Time Frame: 14 months)

	Onasemnogene Abeparvovec-xioi
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant

	adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Number of Participants Analyzed [units: participants]	22
Event-free survival - as compared to the Pediatric Neuromuscular Clinical Research (PNCR) natural history data sets [Neurol. 2014; 83(9):810-817] (units:) Count of Participants (Not Applicable)	

	20 (90.91%)

Statistical Analysis

Groups	Onasemnogene Abeparvovec-xioi	This comparison is made to the results from the age and gender-matched control participants selected from existing natural history data sets (PNCR) [Neurol. 2014; 83(9):810-817].
Non-Inferiority/Equivalence Test	Superiority	6 of 23 participants survived at 14 months from the PNCR historical control dataset.
P Value	<0.0001	
Method	Fisher Exact	

Safety Results

All-Cause Mortality

	Onasemnogene Abeparvovec-xioi N = 22

Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Total participants affected	1 (4.55%)

Serious Adverse Events by System Organ Class

Time Frame	Up to 18 months
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Non-systematic Assessment

	Onasemnogene Abeparvovec-xioi N = 22
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted

	terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Total participants affected	10 (45.45%)
Cardiac disorders	
Cyanosis*	1 (4.55%)
Gastrointestinal disorders	
Dysphagia	1 (4.55%)
Infections and infestations	
Bacterial tracheitis*	1 (4.55%)
Bronchiolitis*	2 (9.09%)
Device related infection*	1 (4.55%)
Pneumonia*	2 (9.09%)
Pneumonia bacterial*	1 (4.55%)
Respiratory syncytial virus bronchiolitis*	2 (9.09%)
Rhinovirus infection*	1 (4.55%)
Sepsis*	1 (4.55%)
Upper respiratory tract infection*	1 (4.55%)

Investigations	
Alanine aminotransferase increased	1 (4.55%)
Aspartate aminotransferase increased	1 (4.55%)
Human metapneumovirus test positive*	1 (4.55%)
Transaminases increased*	1 (4.55%)
Metabolism and nutrition disorders	
Abnormal weight gain	1 (4.55%)
Failure to thrive*	1 (4.55%)
Feeding disorder*	1 (4.55%)
Nervous system disorders	
Hydrocephalus*	1 (4.55%)
Product Issues	
Device malfunction*	1 (4.55%)
Respiratory, thoracic and mediastinal disorders	
Acute respiratory failure*	1 (4.55%)
Atelectasis*	1 (4.55%)
Pneumonia aspiration*	1 (4.55%)
Respiratory arrest*	1 (4.55%)

Respiratory distress*	4 (18.18%)
Respiratory failure	2 (9.09%)

† Systematic Assessment

Other Adverse Events by System Organ Class

Time Frame	Up to 18 months
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Non-systematic Assessment
Frequent Event Reporting Threshold	5%

	Onasemnogene Abeparvovec-xioi N = 22
Arm/Group Description	One-time Intravenous administration of onasemnogene abeparvovec-xioi at the therapeutic dose. Onasemnogene Abeparvovec-xioi: Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene

	under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.
Total participants affected	22 (100.00%)
Blood and lymphatic system disorders	
Thrombocytopenia	2 (9.09%)
Cardiac disorders	
Pericardial effusion	2 (9.09%)
Congenital, familial and genetic disorders	
Asphyxiating thoracic dystrophy*	2 (9.09%)
Cryptorchism*	2 (9.09%)
High arched palate*	2 (9.09%)
Pectus excavatum*	3 (13.64%)

Gastrointestinal disorders	
Abdominal distension*	2 (9.09%)
Constipation*	9 (40.91%)
Diarrhoea*	4 (18.18%)
Dysphagia*	2 (9.09%)
Gastroesophageal reflux disease*	4 (18.18%)
Haematochezia*	2 (9.09%)
Teething*	5 (22.73%)
Vomiting*	4 (18.18%)
General disorders	
Pyrexia*	12 (54.55%)
Infections and infestations	
Conjunctivitis	3 (13.64%)
Gastroenteritis*	2 (9.09%)
Nasopharyngitis*	2 (9.09%)
Otitis media*	3 (13.64%)
Respiratory syncytial virus bronchiolitis*	2 (9.09%)
Upper respiratory tract infection*	11 (50.00%)
Injury, poisoning and procedural complications	
Arthropod bite*	3 (13.64%)
Contusion	4 (18.18%)

Investigations	
Alanine aminotransferase increased*	5 (22.73%)
Aspartate aminotransferase increased*	6 (27.27%)
Blood creatine phosphokinase MB increased*	2 (9.09%)
Gamma-glutamyltransferase increased*	2 (9.09%)
Lymphocyte count decreased*	2 (9.09%)
Weight decreased*	2 (9.09%)
Metabolism and nutrition disorders	
Feeding disorder*	3 (13.64%)
Weight gain poor*	2 (9.09%)
Musculoskeletal and connective tissue disorders	
Deformity thorax*	2 (9.09%)
Joint contracture*	2 (9.09%)
Kyphosis*	2 (9.09%)
Scoliosis*	9 (40.91%)
Torticollis*	2 (9.09%)
Nervous system disorders	

Muscle contractions involuntary	2 (9.09%)
Respiratory, thoracic and mediastinal disorders	
Cough*	7 (31.82%)
Nasal congestion*	3 (13.64%)
Respiration abnormal*	5 (22.73%)
Respiratory distress*	6 (27.27%)
Respiratory track congestion*	2 (9.09%)
Rhinorrhea*	2 (9.09%)
Sleep apnoea syndrome*	3 (13.64%)
Tachypnoea*	3 (13.64%)
Upper respiratory tract congestion*	2 (9.09%)
Use of accessory respiratory muscles*	5 (22.73%)
Skin and subcutaneous tissue disorders	
Dermatitis atopic*	3 (13.64%)
Dermatitis contact*	2 (9.09%)
Dermatitis diaper*	2 (9.09%)
Eczema*	3 (13.64%)
Rash	5 (22.73%)
Urticaria	2 (9.09%)
Vascular disorders	

Diastolic hypertension	2 (9.09%)

† Systematic Assessment

Other Relevant Findings

N/A

Conclusion:

- AVXS-101 demonstrated statistically significant benefits regarding the co-primary endpoint of independent sitting at the 18-month visit).
- Compared to the observations in the Pediatric Neuromuscular Clinical Research (PNCR) natural history data sets [Neurol. 2014; 83(9):810-817], AVXS-101 demonstrated statistically significant benefits regarding the co-primary endpoint of survival without permanent ventilation at 14 months of age.
- The two co-secondary objectives (ability to thrive at 18 months of age and independence of ventilatory support at 18 months of age) were also achieved.
- AVXS-101 was generally well tolerated in this patient population, no new safety signals were identified. The identified and potential risks are monitorable and manageable in patients with 5q Spinal Muscular Atrophy (SMA) given the efficacy associated with AVXS-101 treatment.

Date of Clinical Trial Report

31 March 2020