Sponsor

Novartis Gene Therapies, Inc.

Generic Drug Name

AVXS-101

Trial Indication(s)

Spinal Muscular Atrophy (SMA)

Protocol Number

AVXS-101-CL-304 (COAV101A12303)

Protocol Title

A Global Study of a Single, One-Time Dose of AVXS-101 Delivered to Infants with Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy with Multiple Copies of *SMN2*

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

02 Apr 2018 to 15 Jun 2021

Study Design/Methodology

This was a Phase 3, open-label, single-arm, single-dose study to investigate the efficacy and safety of AVXS-101 in participants who were ≤ 6 weeks (≤ 42 days) of age at the time of gene replacement therapy with pre-symptomatic SMA with bi-allelic deletion of the survival of motor neuron (*SMN*) *1* gene and 2 copies of *SMN2* (Cohort 1) or 3 copies of *SMN2* (Cohort 2) based on genetic diagnosis.

After a maximum 4-week screening period, participants were admitted to the hospital for pre-treatment baseline procedures. Participants received a single, one-time intravenous (IV) infusion of AVXS-101 on Day 1 and underwent inpatient safety monitoring over the next 24 hours. Participants were discharged 24 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Day 3 to End Of Study [EOS]) participants returned at regularly scheduled intervals for efficacy and safety assessments until the EOS when the participant reached 18 months of age (Cohort 1, *SMN2*=2) or 24 months of age (Cohort 2, *SMN2*=3). AVXS-101 was delivered one-time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose of 1.1×10^{14} vector gram per kilogram (vg/kg). Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At Week 9, prednisolone could be discontinued.

The initial protocol planned to enroll 3 cohorts of participants defined by *SMN2* copy number (2, 3, or 4 copies of *SMN2*), however the cohort planned for participants with 4 copies of *SMN2* was removed with protocol amendment 1.

A total of 30 genetically diagnosed and pre-symptomatic SMA participants were enrolled to the study. These included 14 participants enrolled to Cohort 1, and 15 participants enrolled to Cohort 2. In addition, the study enrolled one participant with 4 copies of *SMN2*. This participant underwent the same assessments and follow-up procedures as participants in Cohort 2 for the duration of the study, however the results for this participant are presented separately from the Cohort 1 and Cohort 2 participants and is not reported in this summary due to privacy concerns.

Centers

16 centers in the United States (11 centers), the United Kingdom (1 centers), Belgium (1 centers), Canada (1 center), Australia (1 center), and Japan (1 center).

Objectives:

Primary Objective(s)

Cohort 1: to assess the efficacy of AVXS-101 by demonstrating functional independent sitting for at least 30 seconds as defined by Bayley Scales of Infant and Toddler Development Gross Motor (BSID GM) Subtest Item #26 at any visit up to 18 months of age.

Cohort 2: to assess the efficacy of AVXS-101 based on the proportion of participants achieving the ability to stand without support for at least 3 seconds as defined by BSID GM Subtest Item #40 at any visit up to 24 months of age.

Secondary Objective(s)

Cohort 1: To assess the efficacy of AVXS-101 based on survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 14 months of age.

Cohort 1: To assess the efficacy of AVXS-101 by demonstrating the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age.

Cohort 2: To demonstrate the efficacy of AVXS-101 based the ability to take at least 5 steps independently displaying coordination and balance as defined by BSID GM Subtest Item #43 at any visit up to 24 months of age.

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

One-time IV infusion of AVXS-101 at a dose of 1.1 x 10^{14} vg/kg.

Statistical Methods

All efficacy analyses were conducted using the intention-to-treat (ITT) population as the primary population. These analyses are to test the superiority of AVXS-101 to the results of natural observation studies using the historical data of a population-matched cohort derived from the Pediatric Neuromuscular Clinical Research (PNCR) network (Finkel *et al*. 2014). The ITT population consisted of all enrolled participants with bi-allelic *SMN1* deletions and 2 or 3 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who received AVXS-101. Participants were analyzed according to the assigned *SMN2* copy number cohort. The secondary endpoints for Cohort 1 and Cohort 2 were tested using a hierarchical approach to control for Type I error.

Primary Efficacy - Cohort 1: number of participants who achieved sitting alone for at least 30 seconds (BSID GM Subtest Item #26) at any visit up to the 18 months of age study visit

The number and percentage of participants who achieved the milestone 'sits without support' at any point up to and including the 18 months of age visit were summarized. A one-sided exact binomial test was used to test the null hypothesis of P ≤0.1% at significance level of 0.025, where *P* is the proportion of participants who achieve the milestone of 'sits without support' (BSID GM Subtest item #26). Due to computational considerations the comparison was made to 0.1% in lieu of zero. Furthermore, the corresponding one-sided 97.5% confidence intervals (CI) was estimated by the exact method for binomial proportions.

Primary Efficacy - Cohort 2: number of participants who achieved standing alone for at least 3 seconds (BSID GM Subtest Item #40) at any visit up to 24 months of age

The number and percentage of participants in the study and in the population-matched control cohort of the PNCR network who demonstrate the milestone 'stands alone' at any visit were summarized. Of this cohort, 19/81 (23.5%) of the natural history cohort attained the ability to stand alone (defined as achieving a score of 2 on item #19 of the Hammersmith Functional Motor Scale Expanded (HFMSE)). The actual proportions as well as the difference of the proportions between 2 data sources were summarized and the exact 95% CI provided. The corresponding p-value from a 2-sided Fisher's exact test with α = 0.05 was computed for the comparison between AVXS-101 and PNCR data.

Secondary Efficacy - Cohort 1: event-free survival at 14 months of age, assessed at 14 months of age

Formal testing for the proportion of participants surviving and not requiring permanent ventilation was only to be conducted if the result for the primary endpoint (functional independent sitting) was statistically significant.

The number and percentage of participants in the study and in the population-matched control cohort of the PNCR network surviving event-free to 14 months of age were summarized. The actual proportions as well as the difference of the proportions between 2 data sources were summarized and the exact 95% CI of the difference were provided.

Secondary Efficacy - Cohort 1: number of participants who achieved the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age

Only if the primary endpoint (functional independent sitting) and the first secondary endpoint (survival) for participants with 2 copies of *SMN2* as described above met statistical significance was this second secondary endpoint of ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support to be formally tested.

The number and percentage of participants who maintained weight at or above the third percentile without the need for non-oral/mechanical feeding support at any visit up to the 18 months of age visit were summarized. A one-sided exact binomial test was used to test the null hypothesis of P ≤0.1% at significance level of 0.025, where *P* is the proportion of participants who have achieved the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age. For comparison, the number of participants who maintained the ability to maintain weight at or above the third percentile and/or were independent of ventilatory support at 18 months of age in the PNCR database was essentially zero. Due to computational considerations, the comparison was made to 0.1%. Furthermore, the corresponding one-sided 97.5% CI was estimated by the exact method.

Secondary Efficacy - Cohort 2: number of participants who achieved the ability to walk alone at any visit up to 24 months of age (as defined by BSID GM Subtest Item #43).

Only if the primary endpoint (stands alone) met statistical significance was this secondary endpoint to be formally tested. The number and percentage of participants in the study and in the population-matched control cohort of the PNCR network who demonstrate the milestone ‘walks alone’ at any visit were summarized. Of the population-matched cohort that serves as the comparator in testing the secondary endpoint, 17/81 (21%) attained the ability to walk alone with coordination (defined as achieving a score of 2 on item #20 of the HFMSE). Note that the achievement of a score of 2 on item #20 is not restricted to

occurrences up to 24 months of age in the natural history cohort. The actual proportions as well as the difference of the proportions between 2 data sources were summarized and the exact 95% CI provided. The corresponding p-value from a 2-sided Fisher's exact test with α = 0.05 was computed for the comparison between AVXS-101 and PNCR data.

Safety Analysis: incidence of adverse events (AEs) and/or serious AEs (SAEs)

Safety analyses were conducted on the Safety population for Cohort 1 and Cohort 2 and consisted of all participants who underwent gene therapy infusion.

AEs were presented by primary medical dictionary for regulatory activities (MedDRA) system organ classes and preferred terms and summarized by overall incidence; by the Investigator's assessment as "possibly related, "probably related" or "definitely related" to AVXS-101; by severity; by seriousness; and by whether they led to discontinuation from the study or death.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Age ≤ 6 weeks (≤ 42 days) at time of dose
- Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test
- Compound motor action potential (CMAP) ≥ 2mV at baseline; centralized review of CMAP data were conducted
- Gestational age of 35 to 42 weeks
- Up-to-date on childhood vaccinations that included palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus infections were also recommended in accordance with the guidance of local health authorities. Were able and willing to follow the Consensus Statement for Standard of Care in SMA
- Parent(s)/legal guardian(s) were willing and able to complete the informed consent process and comply with study procedures and visit schedule
- Genetic diagnosis as described below, obtained from an acceptable newborn or pre-natal screening test method:
    - **Cohort 1: Participants with 2 copies of *SMN2* (n ≥14)**
        - Participants with pre-symptomatic SMA Type 1 as determined by the following features:

        - 2 copies of *SMN2*
    - **Cohort 2: Participants with 3 copies of *SMN2* (n ≥12)**
        - Participants with pre-symptomatic SMA Type 2 as determined by the following features:
            - 3 copies of *SMN2.*

Exclusion criteria:

- Weight at screening visit <2 kg
- Hypoxemia (oxygen saturation < 96% awake or asleep without any supplemental oxygen or respiratory support) at the screening visit or for altitudes >1000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit
- Any clinical signs or symptoms at screening or immediately prior to dosing that were, in the opinion of the Investigator, strongly suggestive of SMA (e.g., tongue fasciculation, hypotonia, areflexia)
- Tracheostomy or current prophylactic use or requirement of noninvasive ventilatory support at any time and for any duration prior to screening or during the screening period
- Participants with signs of aspiration/inability to tolerate non thickened liquids based on a formal swallowing test performed as part of screening or participants receiving any non-oral feeding method
- Clinically significant abnormal laboratory values (gammaglutamyl transferase, alanine aminotransferase, and aspartate aminotransferase, or total bilirubin >2 × the upper limit of normal, creatinine ≥1.0 mg/dL, hemoglobin <8 or >18 g/dL; white blood cell >20,000 per cmm) prior to gene replacement therapy. Participants with an elevated bilirubin level that was unequivocally the result of neonatal jaundice should have not been excluded
- Participants with any other clinically significant abnormalities in hematology or clinical chemistry parameters as determined by Investigator or medical monitor
- Treatment with an investigational or commercial product, including nusinersen, given for the treatment of SMA. This included any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation
- Participants whose weight-for-age was below the third percentile
- Biological mother with active viral infection as determined by screening laboratory samples (includes human immunodeficiency virus or positive serology for hepatitis B or C)
    - Biological mothers with clinical suspicion of Zika virus that met Centers for Disease Control and Prevention Zika virus epidemiological criteria including history of residence in or travel to a geographic region with active Zika transmission

at the time of travel were tested for Zika virus ribonucleic acid (RNA). Positive results warrant confirmed negative Zika virus RNA testing in the participant prior to enrolment

- 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 dosing
- Severe non pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator or Sponsor medical monitor, created unnecessary risks for gene replacement therapy such as:
    - Major renal or hepatic impairment
    - Known seizure disorder
    - Diabetes mellitus
    - Idiopathic hypocalciuria
    - Symptomatic cardiomyopathy
- Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
- Previous, planned or expected major surgical procedure including scoliosis repair surgery/procedure during the study assessment period
- 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 4 weeks prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
- Anti-adeno-associated virus 9 (AAV9) antibody titer >1:50 as determined by enzyme-linked immunosorbent assay from biological mother / participant
    - In case of anti-AAV9 antibody titer >1:50, retesting inside the 30-Day screening period was allowed; the participant was eligible to participate if the anti-AAV9 antibody titer upon retesting was ≤1:50, provided the <6 week age requirement at the time of dosing was still met
- Biological mother involved with the care of the child refused anti-AAV9 antibody testing prior to dosing
- 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) refused to sign consent form.

Participant Flow Table (All Participants)

	Cohort 1 n (%)	Cohort 2 n (%)	Total n (%)
Participants who failed screening			14
Participants in the Enrolled population	14 (100.0)	15 (100.0)	29 (100.0)
Participants in the ITT population	14 (100.0)	15 (100.0)	29 (100.0)
Participants in the Safety population	14 (100.0)	15 (100.0)	29 (100.0)
Participants enrolled with the SMN2 gene modifier mutation (c.859G>C)	0	0	0
Participants completed the study	14 (100.0)	15 (100.0)	29 (100.0)
Participants discontinued from the study	0	0	0

Note: Percentages are based on the number of participants enrolled.
Note: Total number of screen failures includes all participants screened for the study, not just those with 3 or 4 copies of SMN2.

Baseline Characteristics (ITT Population)

Characteristic Category/Statistic	Cohort 1 (N = 14)	Cohort 2 (N = 15)
Age at dosing (days)[1]		
n	14	15
Mean (SD)	20.6 (7.87)	28.7 (11.68)
Median (Min, Max)	21.0 (8, 34)	32.0 (9, 43)
0 - 27 days, n (%)	11 (78.6)	6 (40.0)
28 days – 23 months, n (%)	3 (21.4)	9 (60.0)
Gender, n (%)		
Male	4 (28.6)	6 (40.0)
Female	10 (71.4)	9 (60.0)
Ethnicity, n (%)		
Hispanic or Latino	4 (28.6)	2 (13.3)
Not Hispanic or Latino	10 (71.4)	13 (86.7)
Race, n (%)		
Asian	2 (14.3)	2 (13.3)
Black or African American	1 (7.1)	1 (6.7)
White	7 (50.0)	10 (66.7)
Other	4 (28.6)	2 (13.3)

[1] Age at dosing = (dose date − date of birth + 1).

Primary Outcome Result(s)

Number of participants demonstrating independent sitting for 30 seconds at any point up to 18 months of age – Cohort 1 (ITT population)

Time Frame: From Day 1 up to 18 months of age visit

	Cohort 1 (N = 14)
Independent sitting for at least 30 seconds	
n	14
97.5% CI	(76.8, 100.0)
p-value	<.0001
Age when milestone was first demonstrated (months)	
n (%)	14 (100.0)
Mean (SD)	8.21 (1.756)
Median (Min, Max)	8.85 (5.7, 11.8)
Timing of milestone demonstration[1]	
Achieved within normal range, n (%)	11 (78.6)
Achieved but not within normal range, n (%)	3 (21.4)
Did not achieve, n (%)	0

Note: A one-sided exact binomial test was used to test the null hypothesis at significance level of 0.025. The corresponding 97.5% CI was estimated by the exact method for binomial proportions.
Note: The independent sitting milestone is Item #26 “Sits independently for at least 30 seconds” on the Bayley Scales of Infant and Toddler Development Scale.
[1] According to the World Health Organization (WHO) Multicentre Growth Reference Study (MGRS) windows for normal development, the 99th percentile (i.e., upper bound of normal development) of sitting without support was 279 days.

Number of participants achieving the ability to stand without support for at least 3 seconds up to 24 months of age – Cohort 2 (ITT population)
Time Frame: From Day 1 up to 24 months of age visit

	Cohort 2 (N = 15)
Participants achieving milestone, n (%)	15 (100.0)
Age when milestone was first demonstrated (months)	
n	15
Mean (SD)	13.5 (2.18)
Median (Min, Max)	12.6 (9.5, 18.3)
Timing of milestone demonstration [a]	
Achieved within window, n (%)	14 (93.3)
Achieved outside window, n (%)	1 (6.7)
Did not achieve, n (%)	0

[a] According to the WHO-MGRS windows for normal development, the 99th percentile (i.e., upper bound of normal development) of standing alone is 514 days.
Note: The stands without support milestone for AVXS-101 treated participants is determined by Bayley GM Item #40 “Ability to Stand Alone” on the Bayley Scales of Infant and Toddler Development Scale.

Secondary Outcome Result(s)

Number of participants surviving event-free to 14 months of age - Cohort 1 (ITT population)
Time Frame: From Day 1 up to 14 months of age

	Cohort 1 (N = 14)
Event-free survival to 14 months of age, n (%)	14 (100.0)

Note: Participants who terminated the study prior to reaching 14 months of age for any reason were considered treatment failures (event).

Number of participants who maintain weight at or above the third percentile without the need for non-oral/mechanical feeding support to 18 months of age – Cohort 1 (ITT population)
Time Frame: From Day 1 up to 18 months of age

	Cohort 1 (N = 14)
Ability to maintain weight at or above the 3rd percentile without the need for non-oral/mechanical feeding support up to 18 months of age[1]	
n (%)	13 (92.9)
97.5% CI[2]	(66.1, 99.8)
p-value[2]	<.0001
Does not receive nutrition through mechanical support, n (%)	14 (100.0)
Maintains weight consistent with age at all visits, n (%)	13 (92.9)

[1] The ability to maintain weight at or above the 3rd percentile without the need for non-oral/mechanical feeding support is defined as meeting both of the following criteria at all visits: (1) does not receive nutrition through mechanical support (i.e. feeding tube); (2) maintains weight (≥3rd percentile for age and gender as defined by WHO guidelines) consistent with the participant's age at the assessment.
[2] P-value and 97.5% CI are from a one-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% was used in the place of a literal 0.

Number of participants achieving the ability to walk alone up to 24 months of age – Cohort 2 (ITT population)
Time Frame: From Day 1 up to 24 months of age visit

	Cohort 2 (N = 15)
Participants achieving milestone, n (%)	14 (93.3)
Age when milestone was first demonstrated (months)	
n	14
Mean (SD)	14.6 (2.48)
Median (Min, Max)	14.1 (12.1, 18.8)
Timing of milestone demonstration [a]	
Achieved within window, n (%)	11 (73.3)
Achieved outside window, n (%)	3 (20.0)
Did not achieve, n (%)	1 (6.7)

[a] According to the WHO-MGRS windows for normal development, the 99th percentile (i.e., upper bound of normal development) of walking alone is 534 days.
Note: The walks alone with coordination milestone for AVXS-101 treated participants is determined by Bayley GM Item #43 “Ability to Walk Alone” on the Bayley Scales of Infant and Toddler Development Scale.

Other Pre-specified Analysis

Number of participants achieving the ability to stand without support for at least 3 seconds up to 24 months of age – Cohort 2 (ITT population) vs. the data from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014
Time Frame: From Day 1 up to 24 months of age visit

	Cohort 2 (N = 15)		PNCR (N = 81)
Participants achieving milestone, n (%)	15 (100.0)		19 (23.5)
Difference from PNCR (AVXS – PNCR), % (95% CI [a])		76.5 (50.95, 92.21)	
p-value [a]		<0.0001	

Participants from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014, were used as a historical control group for the open-label single-arm AVXS-101-CL-304 (COAV101A12303) study.
[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.
According to the WHO-MGRS windows for normal development, the 99th percentile (i.e., upper bound of normal development) of standing alone is 514 days.
Note: The stands without support milestone for AVXS-101 treated participants is determined by Bayley GM Item #40 "Ability to Stand Alone" on the Bayley Scales of Infant and Toddler Development Scale. The stands alone milestone for PNCR participants is determined by a score of 2 on item #19 of the Hammersmith Functional Motor Scale - Expanded.

Number of participants surviving event-free to 14 months of age - Cohort 1 (ITT population) vs. the data from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014
Time Frame: From Day 1 up to 14 months of age

	Cohort 1 (N = 14)	PNCR (N = 23)	Cohort 1 vs PNCR		
			Difference	95% CI	p-value
Event-free survival to 14 months of age, n (%)	14 (100.0)	6 (26.1)	73.9	44.67, 91.61	<.0001

Participants from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014, were used as a historical control group for the open-label single-arm AVXS-101-CL-304 (COAV101A12303) study.

Note: Exact 95% CI 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.

Note: Participants who terminated the study prior to reaching 14 months of age for any reason were considered treatment failures (event). There was one PNCR participant who met this criterion.

Number of participants achieving the ability to walk alone up to 24 months of age – Cohort 2 (ITT population) vs. the data from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014
Time Frame: From Day 1 up to 24 months of age visit

	Cohort 2 (N = 15)		PNCR (N = 81)
Participants achieving milestone, n (%)	14 (93.3)		17 (21.0)
Difference from PNCR (AVXS – PNCR), % (95% CI [a])		72.3 (44.90, 90.11)	
p-value [a]		<0.0001	

Participants from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014, were used as a historical control group for the open-label single-arm AVXS-101-CL-304 (COAV101A12303) study.

[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.

According to the WHO-MGRS windows for normal development, the 99th percentile (i.e., upper bound of normal development) of walking alone is 534 days.

Note: The walks alone with coordination milestone for AVXS-101 treated participants is determined by Bayley GM Item #43 "Ability to Walk Alone" on the Bayley Scales of Infant and Toddler Development Scale. The walks alone milestone for PNCR participants is determined by a score of 2 on item #20 of the Hammersmith Functional Motor Scale - Expanded.

Safety Results

Serious Adverse Events (SAEs) and Deaths (Safety Population)

Time Frame: Cohort 1: From signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 20 months). Cohort 2: From signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 26 months).

	Cohort 1	**Cohort 2**
No. (%) of subjects studied	14	15
No. (%) of subjects with AE(s)	14 (100.0)	15 (100.0)
Number (%) of subjects with serious or other significant events	n (%)	n (%)
Death	0 (0.0)	0 (0.0)
SAE(s)	5 (35.7)	3 (20.0)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)

Serious Adverse Events by System Organ Class and Preferred Term – Cohort 1 (Safety population)

Time Frame: From signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 20 months).

System organ class Preferred Term	**Cohort 1 (N = 14)** **n (%)**
Ear and labyrinth disorders	1 (7.1)
Middle ear effusion	1 (7.1)
Gastrointestinal disorders	1 (7.1)
Inguinal hernia	1 (7.1)
Infections and infestations	2 (14.3)
Croup infectious	1 (7.1)
Pyelonephritis	1 (7.1)
Metabolism and nutrition disorders	1 (7.1)
Hypercalcaemia	1 (7.1)
Respiratory, thoracic and mediastinal disorders	1 (7.1)
Sleep apnoea syndrome	1 (7.1)

Serious Adverse Events by System Organ Class and Preferred Term – Cohort 2 (Safety population)

Time Frame: From signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 26 months).

System organ class Preferred Term	**Cohort 2 (N = 15)** **n (%)**
Infections and infestations	2 (13.3)
Ear infection	1 (6.7)
Pharyngitis	1 (6.7)
Nervous system disorders	1 (6.7)
Lethargy	1 (6.7)

Non-Serious Treatment-emergent Adverse Events n (%) – 0% Threshold – Cohort 1 (Safety Population)

Time Frame: From Day 1 up to the 18 months of age visit.

System Organ Class Preferred Term	Cohort 1 (N = 14) N (%)
Participants with any TEAE	14 (100.0)
Blood and lymphatic system disorders	
Lymphadenopathy	1 (7.1)
Microcytic anaemia	1 (7.1)
Thrombocytopenia	1 (7.1)
Congenital, familial and genetic disorders	
Dacryostenosis congenital	1 (7.1)
Hydrocele	1 (7.1)
Ear and labyrinth disorders	
Middle ear effusion	1 (7.1)
Endocrine disorders	
Precocious puberty	1 (7.1)
Eye disorders	
Eye discharge	1 (7.1)
Gastrointestinal disorders	
Abdominal discomfort	1 (7.1)
Constipation	4 (28.6)
Diarrhoea	3 (21.4)
Dysphagia	1 (7.1)
Flatulence	1 (7.1)
Gastrooesophageal reflux disease	3 (21.4)
Gingival pain	1 (7.1)
Inguinal hernia	1 (7.1)
Teething	2 (14.3)
Tooth development disorder	1 (7.1)
Vomiting	3 (21.4)
General disorders	
Developmental delay	1 (7.1)
Influenza like illness	1 (7.1)
Malaise	1 (7.1)
Pyrexia	7 (50.0)
Vessel puncture site bruise	1 (7.1)

Immune system disorders	
Food allergy	1 (7.1)
Infections and infestations	
Adenovirus infection	1 (7.1)
COVID-19	1 (7.1)
Candida infection	1 (7.1)
Candida nappy rash	1 (7.1)
Conjunctivitis	1 (7.1)
Croup infectious	1 (7.1)
Ear infection	2 (14.3)
Fungal infection	1 (7.1)
Gastroenteritis viral	1 (7.1)
Infected bite	1 (7.1)
Influenza	2 (14.3)
Nasopharyngitis	2 (14.3)
Otitis media	1 (7.1)
Pneumonia	1 (7.1)
Respiratory tract infection	1 (7.1)
Respiratory tract infection viral	1 (7.1)
Rhinitis	1 (7.1)
Rhinovirus infection	2 (14.3)
Upper respiratory tract infection	5 (35.7)
Viral upper respiratory tract infection	3 (21.4)
Injury, poisoning and procedural complications	
Eye injury	1 (7.1)
Skin abrasion	1 (7.1)
Tracheal deviation	1 (7.1)
Investigations	
Alanine aminotransferase increased	1 (7.1)
Aspartate aminotransferase increased	3 (21.4)
Blood creatine phosphokinase MB increased	1 (7.1)
Blood creatine phosphokinase increased	1 (7.1)
Gamma-glutamyltransferase increased	1 (7.1)
Head lag	1 (7.1)
Platelet count decreased	1 (7.1)
Platelet count increased	1 (7.1)
Troponin increased	1 (7.1)
Metabolism and nutrition disorders	

Failure to thrive	1 (7.1)
Hypercalcaemia	1 (7.1)
Hypomagnesaemia	1 (7.1)
Musculoskeletal and connective tissue disorders	
Hip deformity	1 (7.1)
Joint contracture	1 (7.1)
Kyphosis	1 (7.1)
Loose body in joint	1 (7.1)
Nervous system disorders	
Areflexia	2 (14.3)
Hypertonia	1 (7.1)
Hypokinesia	1 (7.1)
Hyporeflexia	1 (7.1)
Hypotonia	3 (21.4)
Motor developmental delay	1 (7.1)
Muscle contractions involuntary	3 (21.4)
Tremor	3 (21.4)
Psychiatric disorders	
Irritability	1 (7.1)
Renal and urinary disorders	
Nephrocalcinosis	1 (7.1)
Pyelocaliectasis	1 (7.1)
Respiratory, thoracic and mediastinal disorders	
Cough	1 (7.1)
Nasal congestion	3 (21.4)
Rhinorrhoea	1 (7.1)
Sleep apnoea syndrome	1 (7.1)
Snoring	1 (7.1)
Skin and subcutaneous tissue disorders	
Cafe au lait spots	1 (7.1)
Eczema	2 (14.3)
Rash	3 (21.4)

Non-Serious Treatment-emergent Adverse Events n (%) – 0% Threshold – Cohort 2 (Safety Population)

Time Frame: From Day 1 up to the 24 months of age visit.

System Organ Class Preferred Term	Cohort 2 (N = 15) N (%)
Participants with any TEAE	15 (100)
Blood and lymphatic system disorders	
Iron deficiency anaemia	1 (6.7)
Microcytic anaemia	2 (13.3)
Congenital, familial and genetic disorders	
Dacryostenosis congenital	1 (6.7)
Ear and labyrinth disorders	
Ear pain	1 (6.7)
Endocrine disorders	
Cushingoid	1 (6.7)
Eye disorders	
Chalazion	1 (6.7)
Ocular hyperaemia	1 (6.7)
Gastrointestinal disorders	
Abdominal pain upper	1 (6.7)
Constipation	1 (6.7)
Diarrhoea	4 (26.7)
Gastrooesophageal reflux disease	3 (20.0)
Haematemesis	1 (6.7)
Haematochezia	1 (6.7)
Nausea	1 (6.7)
Regurgitation	1 (6.7)
Stomatitis	1 (6.7)
Teething	5 (33.4)
Vomiting	2 (13.3)
General disorders	
Pyrexia	11/15 (73.3)
Infections and infestations	
Bronchitis	1 (6.7)
Conjunctivitis	1 (6.7)
Ear infection	1 (6.7)

Exanthema subitum	1 (6.7)
Fungal skin infection	1 (6.7)
Gastroenteritis	2 (13.3)
Hand-foot-and-mouth disease	2 (13.3)
Nasopharyngitis	3 (20.0)
Otitis media	3 (20.0)
Otitis media acute	1 (6.7)
Respiratory syncytial virus infection	1 (6.7)
Respiratory tract infection viral	1 (6.7)
Rhinitis	1 (6.7)
Roseola	1 (6.7)
Upper respiratory tract infection	9 (60.0)
Urinary tract infection	2 (13.3)
Viral infection	1 (6.7)
Viral upper respiratory tract infection	1 (6.7)
Injury, poisoning and procedural complications	
Arthropod sting	1 (6.7)
Contusion	1 (6.7)
Eyelid injury	1 (6.7)
Scratch	1 (6.7)
Skin wound	1 (6.7)
Investigations	
Alanine aminotransferase increased	3 (20.0)
Aspartate aminotransferase increased	4 (26.7)
Bacterial test positive	1 (6.7)
Blood alkaline phosphatase increased	1 (6.7)
Blood calcium increased	2 (13.3)
Blood creatine phosphokinase MB increased	2 (13.3)
Carbon dioxide decreased	1 (6.7)
Gamma-glutamyltransferase increased	1 (6.7)
Platelet count increased	1 (6.7)
Troponin increased	2 (13.3)
Metabolism and nutrition disorders	
Lactose intolerance	1 (6.7)
Poor feeding infant	1 (6.7)
Weight gain poor	1 (6.7)
Musculoskeletal and connective tissue disorders	
Pain in extremity	1 (6.7)

Nervous system disorders	
Areflexia	1 (6.7)
Febrile convulsion	1 (6.7)
Hypotonia	2 (13.3)
Lethargy	1 (6.7)
Muscle contractions involuntary	1 (6.7)
Psychiatric disorders	
Agitation	1 (6.7)
Irritability	1 (6.7)
Renal and urinary disorders	
Dysuria	1 (6.7)
Respiratory, thoracic and mediastinal disorders	
Cough	4 (26.7)
Nasal congestion	2 (13.3)
Upper respiratory tract congestion	1 (6.7)
Skin and subcutaneous tissue disorders	
Blister	1 (6.7)
Dermatitis diaper	3 (20.0)
Eczema infantile	1 (6.7)
Lipohypertrophy	1 (6.7)
Miliaria	1 (6.7)
Pruritus	1 (6.7)
Rash	2 (13.3)
Rash macular	1 (6.7)

Overview of Treatment-emergent Adverse Events (TEAEs) – Cohort 1 (Safety population)

Time Frame: TEAEs were collected from Day 1 up to the 18 months of age visit. SAEs were collected from signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 20 months).

Adverse event category	**Cohort 1 (N = 14) n (%)**
Any TEAE	14 (100.0)
TEAEs related to study treatment[1]	10 (71.4)
TEAEs of Grade 3 severity or higher	4 (28.6)
Serious TEAEs	5 (35.7)
Serious TEAEs related to study treatment[1]	0
TEAEs leading to study discontinuation	0
TEAEs leading to death	0

[1] TEAEs were considered related to treatment if they were classified by the Investigator as possibly, probably, or definitely related to study treatment.

Overview of Treatment-emergent Adverse Events – Cohort 2 (Safety population)

Time Frame: TEAEs were collected from Day 1 up to the 24 months of age visit. SAEs were collected from signing of informed consent to 30 days after the last study visit (up to a maximum of approximately 26 months).

Adverse event category	**Cohort 2 (N = 15) n (%)**
Any TEAE	15 (100.0)
TEAEs related to study treatment[1]	8 (53.3)
TEAEs of Grade 3 severity or higher	3 (20.0)
Serious TEAEs	3 (20.0)
Serious TEAEs related to study treatment[1]	0
TEAEs leading to study discontinuation	0
TEAEs leading to death	0

[1] TEAEs were considered related to treatment if they were classified by the Investigator as possibly, probably, or definitely related to study treatment.

Conclusion:

The following conclusions can be made regarding the efficacy and safety of AVXS-101 based on observations made in Cohort 1 and Cohort 2 of this study:

- Cohort 1: AVXS-101 gene therapy provided therapeutic benefits to pre-symptomatic participants with bi-allelic deletions of the *SMN1* gene and 2 copies of the *SMN2* gene, in comparison to data from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014.

- Cohort 2: AVXS-101 gene therapy provided therapeutic benefits to pre-symptomatic participants with bi-allelic deletions of the *SMN1* gene and 3 copies of the *SMN2* gene, in comparison to data from the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014.

- Cohorts 1 and 2: AVXS-101 was generally well tolerated in both participant populations, and no new safety signals were identified in this study. The safety findings were consistent between the 2 cohorts. Identified and potential risks for this investigational product are manageable in participants with SMA, and given the substantial efficacy associated with AVXS-101 treatment, compared to the observational study, Pediatric Neuromuscular Clinical Research Network (PNCR), Finkel et al, 2014, the benefit-risk profile is favorable for both cohorts.

Date of Clinical Study Report

05 October 2021