Sponsor

Novartis Gene Therapies, Inc.

Generic Drug Name

AVXS-101/OAV101 (onasemnogene abeparvovec)

Trial Indication(s)

Spinal muscular atrophy Type 2/3

Protocol Number

AVXS-101-CL-102 (COAV101A12102)

Protocol Title

Phase 1, Open-Label, Dose Comparison Study of AVXS-101 for Sitting but Non-Ambulatory Patients with Spinal Muscular Atrophy

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

21 Dec 2017 to 18 Nov 2021

Reason for Termination

Novartis Gene Therapies, Inc. terminated the study as this study had met its overall strategic objectives within the broader intrathecal clinical development program, and the decision was made not to enroll further participants into Cohort 3.

Study Design/Methodology

AVXS-101-CL-102 was a Phase 1, open-label, ascending dose, historically controlled study to assess the efficacy, safety, and tolerability of a single dose of AVXS-101 administered intrathecally (IT) in children 6 to <60 months of age with a genetic diagnosis consistent with spinal muscular atrophy (SMA), bi-allelic deletion of *SMN1* and 3 copies of *SMN2* without the genetic modifier who are able to sit but cannot stand or walk unassisted at the time of study entry. Participants were stratified in 2 groups, based on age at dosing: 6 to <24 months of age, and 24 to <60 months of age.

After a 60-day baseline and screening interval, participants were administered AVXS-101 as a single IT injection. Three dose levels were evaluated: 6.0E13 vg (Cohort 1); 1.2E14 vg (Cohort 2); 2.4E14 vg (Cohort 3). The duration of follow-up post IT administration was 12 months for Cohorts 1 and 2, and 15 months for Cohort 3.

The study planned to evaluate up to 3 different doses of AVXS-101 IT in consecutive dose cohorts of participants. After enrollment into Cohorts 1 and 2 was completed, and enrollment into Cohort 3 was initiated, the Food and Drug Administration (FDA) imposed a partial clinical hold on the AVXS-101 investigational new drug (IND) (intrathecal program) due to safety concerns following non-human primate dorsal root ganglia findings. Enrollment into the study was suspended, at which time only 4 participants (out of 24 planned) were enrolled to Cohort 3. After the partial clinical hold was lifted, Novartis Gene Therapies determined that this study had met its overall strategic objectives within the broader intrathecal clinical development program, and the decision was made not to enroll further participants into Cohort 3.

Centers

11 centers in the United States.

Objectives:

Primary objective(s)

To assess the safety and tolerability of IT administration of AVXS-101 by the incidence and severity of adverse events (AEs) while determining the optimal dose of AVXS-101 that demonstrates acceptable safety administered by IT injection.

Participants ≥6 months and <24 months of age at time of dosing: To determine the proportion of participants achieving the ability to stand without support for at least 3 seconds (Bayley Scales of Infant and Toddler Development – Gross Motor (GM) Subtest Item #40).

Participants ≥24 months and <60 months of age at time of dosing: To determine the change from baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE).

Secondary objective

The secondary efficacy objective for both age groups was to determine the proportion of participants that achieved ability to walk without assistance, defined as taking at least 5 steps independently displaying coordination and balance (Bayley Scales of Infant and Toddler Development – GM Subtest Item #43).

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

One-time IT injection of AVXS-101. Three dose levels were evaluated:

- Cohort 1: 6.0E13 vg
- Cohort 2: 1.2E14 vg
- Cohort 3: 2.4E14 vg

Statistical Methods

The safety and tolerability of IT administration of AVXS-101 was assessed through the incidence and severity of AEs through the last study visit (12 months for Cohorts 1 and 2 and 15 months for Cohort 3). The proportion of participants with any AE, any serious AE; any AE related to study product, and any Grade III or higher AE was summarized overall, and by Body System and Preferred Term. Incidence rates were also reported by cohort.

The primary safety evaluations were performed on the safety analysis set (defined as all participants given an AVXS-101 IT injection. Participants were analyzed according to actual dose received).

The primary efficacy endpoints were:

- Participants ≥6 to <24 months of age at time of dosing: proportion of treated participants who achieve the motor milestone stands alone (Bayley-III GM Subtest item # 40) at any post-treatment visit up to the 12-month study visit.
- Participants ≥24 to <60 months of age at time of dosing: change from baseline in HFMSE in treated participants at the 12-month study visit.

The secondary efficacy endpoint for both age groups was the proportion of participants achieving the motor milestone walks alone (Bayley Scales of Infant and Toddler Development – GM Subtest Item #43) at any post-treatment visit up to the 12-month study visit.

A population-matched historical control cohort was drawn from the Pediatric Neuromuscular Clinical Research (PNCR) Natural History dataset. The following populations were chosen for analysis purposes:

- For comparison with participants ≥6 to <24 months of age: participants with SMA Types 2 or 3, 3 copies of *SMN2*, symptom onset before 12 months of age, and had at least one visit at or before 36 months of age was designated as the “population-matched” control cohort (N=51).
- For comparison with participants ≥24 to <60 months of age: participants with SMA Types 2 or 3, 3 copies of *SMN2*, symptom onset before 12 months of age, diagnosis before 24 months of age, unable to stand or walk unassisted at enrollment (baseline visit), received a HFMSE evaluation between 24 and 60 months of age (“baseline”), and a follow-up evaluation (Hammersmith Functional Motor Scale [HFMS] or HFMSE) performed between 12 and 14 months following that baseline evaluation (N=15). This group is referred to as the *Primary PNCR* population. A

second subset of participants was identified to improve matching between the participant group and the natural history controls, and is referred to as the *Sensitivity PNCR* population (N=17).

For both age groups, the comparisons of primary and secondary categorical endpoints in proportions between Cohort 2 and the PNCR data were summarized by differences in response rates with 95% confidence intervals (CIs). Two-sided tests were performed to test the null hypothesis at a significance level of 5%.

For participants 24 to <60 months of age, a two-sided test at a significance level of 5% was performed to test the null hypothesis for the primary endpoint.

The primary and secondary efficacy evaluations were performed on the intent-to-treat (ITT) population (defined as all enrolled participants who were given an AVXS-101 IT injection. Participants were analyzed according to the assigned dose).

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Participants ≥6 months and up to 60 months (1800 days) of age at time of dosing following diagnostic confirmation during screening period by genotype who demonstrate the ability to sit unassisted for 10 or more seconds but cannot stand or walk independently.
- Diagnostic confirmation by genotype includes lab documentation of homozygous absence of *SMN1* exon 7; with exactly 3 copies of *SMN2.*
- Negative gene testing for *SMN2* gene modifier mutation (c.859G>C).
- Onset of clinical signs and symptoms consistent with SMA at < 12 months of age.
- Able to sit independently and not standing or walking independently. Definition of sitting independently is defined by the World Health Organization Multicentre Growth Reference Study (WHO-MGRS) criteria of being able to sit up unsupported with head erect for at least 10 seconds. Child should not use arms or hands to balance body or support position (Wijnhoven 2004).
- Be up-to-date on childhood vaccines that include palivizumab prophylaxis (also known as Synagis®) to prevent respiratory syncytial virus infections are also recommended in accordance with American Academy of Pediatrics (AAP 2009).

Key Exclusion Criteria

- Current or historical ability to stand or walk independently.
- Contraindications for spinal tap procedure or administration of IT therapy or presence of an implanted shunt for the drainage of cerebrospinal fluid (CSF) or an implanted central venous (CNS) catheter.
- Severe contractures as determined by designated Physical Therapist(s) at screening that interfere with either the ability to attain/demonstrate functional measures or interferes with ability to receive IT dosing.
- Severe scoliosis (defined as ≥ 50° curvature of spine) evident on X-ray examination.
- Previous, planned or expected scoliosis repair surgery/procedure within 1 year of dose administration.
- Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening while the participant is awake, or for high altitudes > 1000 m, oxygen saturation < 92% while the participant is awake.
- Pulse oximetry saturation must not decrease ≥ 4 percentage points between screening and highest value on day of dosing.
- Use or requirement of non-invasive ventilatory support for 12 or more hours daily over the 2 weeks prior to dosing.
- Medical necessity for a gastric feeding tube, where the majority of feedings are given by non-oral methods (i.e., nasogastric tube or nasojejunal tube) or participants whose weight-for-age falls below the 3rd percentile based on World Health Organization (WHO) Child Growth Standards (Onis 2006). Placement of a permanent gastrostomy prior to screening is not an exclusion.
- Use or requirement of non-invasive ventilatory support for 12 or more hours daily over the 2 weeks prior to dosing.
- Medical necessity for a gastric feeding tube, where the majority of feedings are given by non-oral methods or participants whose weight-for-age falls below the 3rd percentile based on WHO Child Growth Standards (Onis 2006). Placement of a permanent gastrostomy prior to screening is not an exclusion.
- Active viral infection (includes human immunodeficiency virus or serology positive for hepatitis B or C, or Zika virus).
- Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to study entry.
- Respiratory infection requiring medical attention, medical intervention or increase in supportive care of any manner within 4 weeks prior to study entry.
- Severe non-pulmonary/respiratory tract infection within 4 weeks before study dosing or concomitant illness that in the opinion of the Principal Investigator creates unnecessary risks for gene transfer such as:

  - Major renal or hepatic impairment.
  - Known seizure disorder.
  - Diabetes mellitus.
  - Idiopathic hypocalciuria.
  - Symptomatic cardiomyopathy.
- History of bacterial meningitis or brain or spinal cord disease, including tumors, or abnormalities by magnetic resonance imaging or computerized tomography that would interfere with the lumbar puncture procedures or CSF circulation.
- Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients.
- Known allergy or hypersensitivity to iodine or iodine-containing products.
- 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, or immunosuppressive therapy within 3 months of study dosing.
- Inability to withhold use of laxatives or diuretics in the 24 hours prior to dose administration.
- Anti- adeno-associated virus 9 (AAV9) antibody titers >1:50 as determined by enzyme-linked immunosorbent assay 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-glutamyltransferase [GGT], alanine aminotransferase [ALT], and aspartate aminotransferase [AST], or total bilirubin > 2 × upper limit of normal [ULN], creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm^3) prior to gene replacement therapy. Participants with an elevated bilirubin level that is unequivocally the result of neonatal jaundice shall not be excluded.
- Participation in recent SMA treatment clinical trial or receipt of an investigational or approved compound product or therapy received with the ITT SMA at any time prior to screening for this study.
  - Oral beta agonists must be discontinued 30 days prior to 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 1-year study assessment period.

Participant Flow Table (All Participants)

	AVXS-101 IT					
	Cohort 1 6.0E13 vg	Cohort 2 1.2E14 vg		Cohort 3 2.4E14 vg		All participants
	Age 6 to <24 months	Age 6 to <24 months	Age 24 to <60 months	Age 6 to <24 months	Age 24 to <60 months	
	N=3	N=13	N=12	N=4	N=0	N=32
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Disposition						
Received AVXS-101 IT injection	3 (100)	13 (100)	12 (100)	4 (100)	0	32 (100)
Completed the study	3 (100)	13 (100)	12 (100)	4 (100)	0	32 (100)
Participants completed the study within 30 days of when last study visit was scheduled to occur	3 (100)	13 (100)	12 (100)	1 (25.0)	0	29 (90.6)
Participants completed the study more than 30 days after when last study visit was scheduled to occur	0	0	0	3 (75.0)	0	3 (9.4)
Discontinued from the study	0	0	0	0	0	0

IT = intrathecal.

Note: Percentages are based on the number of participants enrolled.

Baseline Characteristics (Safety Analysis Set)

	AVXS-101 IT				
	Cohort 1 6.0E13 vg	Cohort 2 1.2E14 vg		Cohort 3 2.4E14 vg	All participants
	Age 6 to <24 months	Age 6 to <24 months	Age 24 to <60 months	Age 6 to <24 months	
	N=3	N=13	N=12	N=4	N=32
Age at baseline (months) [1]					
Mean (SD)	17.2 (4.1)	16.7 (4.5)	37.5 (10.6)	16.9 (5.6)	24.6 (12.5)
Median (Min, Max)	18.9 (13, 20)	17.7 (7, 23)	33.7 (26, 55)	17.4 (10, 23)	20.3 (7, 55)
Sex, n (%)					
Male	1 (33.3)	7 (53.8)	6 (50.0)	4 (100.0)	18 (56.3)
Female	2 (66.7)	6 (46.2)	6 (50.0)	0	14 (43.8)
Race, n (%)					
White	2 (66.7)	10 (76.9)	8 (66.7)	3 (75.0)	23 (71.9)
Asian	0	1 (7.7)	4 (33.3)	1 (25.0)	6 (18.8)
Other	0	1 (7.7)	0	0	1 (3.1)
Multiple	1 (33.3)	1 (7.7)	0	0	2 (6.3)
Ethnicity, n (%)					
Hispanic or Latino	2 (66.7)	3 (23.1)	0	0	5 (15.6)
Not Hispanic or Latino	1 (33.3)	10 (76.9)	12 (100)	4 (100)	27 (84.4)

IT = Intrathecal.
[1] Age = (date of study drug administration - date of birth + 1)/30, rounded to 1st decimal.

Primary Outcome Result(s)

Participants 6 to <24 months of age at time of dosing: proportion of treated participants who achieve the motor milestone stands alone (Bayley-III GM Subtest item # 40) at any post-treatment visit up to the 12-month study visit (ITT Population)
Time Frame: From Day 1 up to Month 12.

	AVXS-101 IT		
	Cohort 1 6.0E13 vg N=3	Cohort 2 1.2E14 vg N=13	Cohort 3 2.4E14 vg N=4
Proportion of participants achieving the ability to stand alone, n (%)			
Yes	1 (33.3)	1 (7.7)	0
No	2 (66.7)	12 (92.3)	4 (100)

IT = Intrathecal

Participants 24 to <60 months of age at time of dosing: change from baseline in HFMSE in treated participants at the 12-month study visit (ITT Population)
Time Frame: Baseline and Month 12.

	AVXS-101 IT Cohort 2, 1.2E14 vg N=12
Baseline	
n	12
Mean (SD)	14.8 (9.98)
Median (Min, Max)	12.0 (3, 32)
Month 12: actual value	
n	12
Mean (SD)	21.3 (11.94)
Median (Min, Max)	16.5 (6, 40)
Month 12: change from baseline	
n	12
Mean (SD)	6.6 (7.34)

IT = Intrathecal

Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE) (Safety Analysis Set)

Time Frame: Adverse events were collected from the single dose of study treatment until the end of study visit (12 months for Cohort 1 and 2 and 15 months for Cohort 3).

	AVXS-101 IT			
	Cohort 1 6.0E13 vg Age 6 to <24 Months	**Cohort 2 1.2E14 vg Age 6 to <24 Months**	**Cohort 2 1.2E14 vg Age 24 to <60 Months**	**Cohort 3 2.4E14 vg Age 6 to <24 Months**
	N=3	**N=13**	**N=12**	**N=4**
TEAE	3 (100.0)	13 (100.0)	12 (100.0)	4 (100.0)
Serious TEAE	1 (33.3)	2 (15.4)	4 (33.3)	0
TEAE Related to AVXS-101	0	7 (53.9)	4 (33.3)	1 (25.0)
TEAE with CTCAE Grade ≥ 3	1 (33.3)	4 (30.8)	4 (33.3)	0

A TEAE was defined as any event that began or worsened in severity on or after the administration of AVXS-101 through the last study visit.

CTCAE = Common Terminology Criteria for Adverse Events (grade 3 = severe or medically significant to grade 5 = death related to TEAE)

Secondary Outcome Result(s)

Proportion of participants achieving the motor milestone walks alone (Bayley-III GM Subtest item # 43) at any post-treatment visit up to the 12-month study visit (ITT Population)
Time Frame: From Day 1 up to Month 12.

	AVXS-101 IT			
	Cohort 1 6.0E13 vg Age 6 to <24 Months N=3	**Cohort 2 1.2E14 vg Age 6 to <24 Months N=13**	**Cohort 2 1.2E14 vg Age 24 to <60 Months N=12**	**Cohort 3 2.4E14 vg Age 6 to <24 Months N=4**
Proportion of participants achieving the ability to walk alone, n (%)				
Yes	0	1 (7.7)	0	0
No	3 (100.0)	12 (92.3)	12 (100.0)	4 (100)

IT = Intrathecal.

Average Number of Hours Per Day of Non-invasive Ventilatory Support
Time Frame: Months 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

	AVXS-101 IT			
	Cohort 1 6.0E13 vg Age 6 to <24 Months N=0	**Cohort 2 1.2E14 vg Age 6 to <24 Months N=1**	**Cohort 2 1.2E14 vg Age 24 to <60 Months N=1**	**Cohort 3 2.4E14 vg Age 6 to <24 Months N=0**
Average Number of Hours Per Day of Non-invasive Ventilatory Support (hours/day)				
Month 2	NA	NA	10.530	NA
Month 3	NA	NA	2.930	NA
Month 4	NA	0.000	5.860	NA
Month 5	NA	0.000	4.610	NA
Month 6	NA	2.590	4.490	NA
Month 7	NA	4.550	7.490	NA
Month 8	NA	7.170	8.290	NA
Month 9	NA	8.690	7.690	NA
Month 10	NA	10.320	9.900	NA
Month 11	NA	14.050	3.460	NA
Month 12	NA	10.120	0.040	NA

IT = Intrathecal. Data were only collected in participants requiring BiPAP support.

Other Pre-specified Analysis

Comparison of the number of participants 6 to <24 months of age at time of dosing: proportion of treated participants who achieve the motor milestone stands alone (Bayley-III GM Subtest item # 40) at any post-treatment visit up to the 12-month study visit v. the population-matched natural history Pediatric Neuromuscular Clinical Research Network (PNCR) control study (ITT Population)

Time Frame: From Day 1 up to Month 12.

	PNCR	AVXS-101 IT		
		Cohort 1 6.0E13 vg	Cohort 2 1.2E14 vg	Cohort 3 2.4E14 vg
	N=51	N=3	N=13	N=4
Proportion of participants achieving the ability to stand alone, n (%)				
Yes	7 (13.7)	1 (33.3)	1 (7.7)	0
No	44 (86.3)	2 (66.7)	12 (92.3)	4 (100)
Proportion difference test [1]				
Difference in percent vs PNCR (95% CI)			-6.0 (-21.8, 22.8)	
p-value (Fisher's exact test)			>0.9999	

IT = Intrathecal; PNCR = Pediatric Neuromuscular Clinical Research.
[1] The p-value is from a Fisher's exact test for the comparison between Cohort 2 and PNCR data.

Comparison of the number of participants 24 to <60 months of age at time of dosing: change from baseline in HFMSE in treated participants at the 12-month study visit v. the population-matched natural history PNCR control study (ITT Population)
Time Frame: Baseline and Month 12.

	Primary PNCR N=15	AVXS-101 IT Cohort 2, 1.2E14 vg N=12
Baseline		
n	15	12
Mean (SD)	11.8 (7.34)	14.8 (9.98)
Median (Min, Max)	9.0 (0, 22)	12.0 (3, 32)
Month 12: actual value		
n	9	12
Mean (SD)	10.2 (7.36)	21.3 (11.94)
Median (Min, Max)	10.0 (0, 22)	16.5 (6, 40)
Month 12: change from baseline		
n	9	12
Mean (SD)	0.8 (2.86)	6.6 (7.34)
MMRM [1]		
LS Mean (95% CI)	0.5 (-2.2, 3.2)	6.0 (3.7, 8.3)
Difference between LS mean (95% CI)		5.5 (1.9, 9.0)
p-value		0.0027

IT = Intrathecal; CI = Confidence Interval; LS = Least Square; PNCR = Pediatric Neuromuscular Clinical Research; MMRM = Mixed Model with Repeated Measurement Analysis.

[1] The analysis is using a mixed model with repeated measurement. The model includes the change from baseline as the dependent variable, fixed effect of cohort (AVXS-101 and PNCR), visit, covariates of Baseline HFMSE and age at baseline, and interactions of cohort*age at baseline, baseline HFMSE*visit, Baseline HFMSE*cohort, and cohort*visit. A compound symmetry covariance structure is assumed initially to model the within-participant errors.

Note: The Primary PNCR group is the comparator group defined per protocol.

Comparison of the proportion of participants achieving the motor milestone walks alone (Bayley-III GM Subtest item # 43) at any post-treatment visit up to the 12-month study visit v. the population-matched natural history PNCR control study (ITT Population)
Time Frame: From Day 1 up to Month 12.

	PNCR	AVXS-101 IT			
		Cohort 1 6.0E13 vg Age 6 to <24 Months	Cohort 2 1.2E14 vg Age 6 to <24 Months	Cohort 2 1.2E14 vg Age 24 to <60 Months	Cohort 3 2.4E14 vg Age 6 to <24 Months
	N=51	N=3	N=13	N=12	N=4
Proportion of participants achieving the ability to walk alone, n (%)					
Yes	5 (9.8)	0	1 (7.7)	0	0
No	46 (90.2)	3 (100.0)	12 (92.3)	12 (100.0)	4 (100)
Proportion difference test [1]					
Difference in proportions vs PNCR (95% CI)			-2.1 (-17.2, 27.0)		
p-value (Fisher's exact test)			>0.9999		

IT = Intrathecal; PNCR = Pediatric Neuromuscular Clinical Research.
[1] The p-value is from a Fisher's exact test for the comparison between Cohort 2 (age 6 to <24 months) and PNCR data.

Safety Results

Serious Adverse Events and Deaths (Safety Population)

Time Frame: Adverse events were collected from the single dose of study treatment until the end of study visit (12 months for Cohort 1 and 2 and 15 months for Cohort 3).

	AVXS-101 IT			
	Cohort 1 6.0E13 vg	**Cohort 2 1.2E14 vg**	**Cohort 2 1.2E14 vg**	**Cohort 3 2.4E14 vg**
	Age 6 to <24 months	**Age 6 to <24 months**	**Age 24 to <60 months**	**Age 6 to <24 months**
No. of participants studied	3	13	12	4
No. (%) of participants with AE(s)	3 (100)	13 (100)	12 (100)	4 (100)
Number (%) of participants with serious or other significant events	n (%)	n (%)	n (%)	n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)	1 (33.3)	2 (15.4)	4 (33.3)	0
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

IT = Intrathecal.

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

Time Frame: Adverse events were collected from the single dose of study treatment until the end of study visit (12 months for Cohort 1 and 2 and 15 months for Cohort 3).

	AVXS-101 IT			
	Cohort 1 6.0E13 vg	Cohort 2 1.2E14 vg	Cohort 2 1.2E14 vg	Cohort 3 2.4E14 vg
	Age 6 to <24 months	Age 6 to <24 months	Age 24 to <60 months	Age 6 to <24 months
System Organ Class	(N=3)	(N=13)	(N=12)	(N=4)
Preferred Term	n (%)	n (%)	n (%)	n (%)
Infections and infestations	0	0	4 (33.3)	0
Bronchitis	0	0	1 (8.3)	0
Influenza	0	0	1 (8.3)	0
Pneumonia	0	0	1 (8.3)	0
Pneumonia respiratory syncytial viral	0	0	1 (8.3)	0
Respiratory tract infection viral	0	0	1 (8.3)	0
Rhinovirus infection	0	0	1 (8.3)	0
Investigations	1 (33.3)	2 (15.4)	0	0
Blood alkaline phosphatase increased	1 (33.3)	1 (7.7)	0	0
Alanine aminotransferase increased	0	1 (7.7)	0	0
Aspartate aminotransferase increased	0	1 (7.7)	0	0
Respiratory, thoracic and mediastinal disorders	1 (33.3)	0	2 (16.7)	0
Acute respiratory failure	0	0	1 (8.3)	0
Asthma	0	0	1 (8.3)	0
Respiratory failure	1 (33.3)	0	0	0

IT = Intrathecal.

Other Adverse Events (Non-Serious Adverse Events) by System Organ Class and Preferred Term (Safety Population) – 0% Threshold

Time Frame: Adverse events were collected from the single dose of study treatment until the end of study visit (12 months for Cohort 1 and 2 and 15 months for Cohort 3).

	AVXS-101 IT			
	Cohort 1 6.0E13 vg	Cohort 2 1.2E14 vg	Cohort 2 1.2E14 vg	Cohort 3 2.4E14 vg
System Organ Class Preferred Term	Age 6 to <24 months (N=3) n (%)	Age 6 to <24 months (N=13) n (%)	Age 24 to <60 months (N=12) n (%)	Age 6 to <24 months (N=4) n (%)
Blood and lymphatic system disorders	0	3 (23.1)	1 (8.3)	0
Lymphadenopathy	0	2 (15.4)	1 (8.3)	0
Leukopenia	0	1 (7.7)	0	0
Cardiac disorders	0	4 (30.8)	5 (41.7)	0
Tachycardia	0	2 (15.4)	2 (16.7)	0
Mitral valve incompetence	0	1 (7.7)	1 (8.3)	0
Sinus tachycardia	0	1 (7.7)	1 (8.3)	0
Cardiomegaly	0	0	1 (8.3)	0
Pericardial effusion	0	1 (7.7)	0	0
Pulmonary valve incompetence	0	0	1 (8.3)	0
Congenital, familial and genetic disorders	0	2 (15.4)	0	0
Pectus carinatum	0	1 (7.7)	0	0
Pectus excavatum	0	1 (7.7)	0	0
Ear and labyrinth disorders	0	0	2 (16.7)	0
Ear discomfort	0	0	1 (8.3)	0
Motion sickness	0	0	1 (8.3)	0

Endocrine disorders	0	0	1 (8.3)	0
Cushingoid	0	0	1 (8.3)	0
Gastrointestinal disorders	1 (33.3)	9 (69.2)	6 (50.0)	4 (100.0)
Vomiting	0	5 (38.5)	3 (25.0)	2 (50.0)
Constipation	0	2 (15.4)	3 (25.0)	2 (50.0)
Teething	1 (33.3)	2 (15.4)	0	1 (25.0)
Abdominal pain	0	0	1 (8.3)	0
Anal fissure	0	1 (7.7)	0	0
Dental caries	0	0	1 (8.3)	0
Diarrhoea	0	1 (7.7)	0	0
Dysphagia	0	0	0	1 (25.0)
Gastrooesophageal reflux disease	0	1 (7.7)	0	0
Haematochezia	0	1 (7.7)	0	0
Tooth resorption	0	1 (7.7)	0	0
General disorders and administration site conditions	3 (100)	6 (46.2)	7 (58.3)	2 (50.0)
Pyrexia	3 (100)	6 (46.2)	7 (58.3)	2 (50.0)
Application site irritation	0	1 (7.7)	0	0
Infusion site bruising	1 (33.3)	0	0	0
Hepatobiliary disorders	0	1 (7.7)	0	0
Hepatomegaly	0	1 (7.7)	0	0
Immune system disorders	1 (33.3)	0	1 (8.3)	1 (25.0)
Seasonal allergy	0	0	1 (8.3)	1 (25.0)
Hypersensitivity	1 (33.3)	0	0	0
Infections and infestations	2 (66.7)	11 (84.6)	11 (91.7)	4 (100.0)
Upper respiratory tract infection	2 (66.7)	10 (76.9)	5 (41.7)	3 (75.0)
Nasopharyngitis	0	3 (23.1)	2 (16.7)	1 (25.0)
Otitis media	1 (33.3)	0	3 (25.0)	0

Viral infection	0	1 (7.7)	1 (8.3)	1 (25.0)
Conjunctivitis	0	2 (15.4)	0	0
Ear infection	0	1 (7.7)	1 (8.3)	0
Pneumonia	1 (33.3)	0	1 (8.3)	0
Bacteriuria	0	0	1 (8.3)	0
Coxsackie viral infection	0	0	0	1 (25.0)
Croup infectious	0	0	0	1 (25.0)
Furuncle	0	1 (7.7)	0	0
Gastroenteritis	0	0	1 (8.3)	0
Gastroenteritis viral	0	0	0	1 (25.0)
Metapneumovirus infection	1 (33.3)	0	0	0
Parainfluenzae virus infection	0	0	1 (8.3)	0
Pharyngitis	0	0	1 (8.3)	0
Pharyngitis streptococcal	0	1 (7.7)	0	0
Respiratory tract infection viral	0	0	1 (8.3)	0
Rhinovirus infection	0	0	1 (8.3)	0
Viral pharyngitis	0	1 (7.7)	0	0
Viral rash	0	1 (7.7)	0	0
Viral upper respiratory tract infection	0	0	1 (8.3)	0
Injury, poisoning and procedural complications	0	5 (38.5)	3 (25.0)	0
Arthropod bite	0	3 (23.1)	0	0
Contusion	0	2 (15.4)	0	0
Skin abrasion	0	0	2 (16.7)	0
Fall	0	0	1 (8.3)	0
Investigations	1 (33.3)	9 (69.2)	2 (16.7)	2 (50.0)
Blood alkaline phosphatase increased	0	2 (15.4)	0	1 (25.0)
Activated partial thromboplastin time prolonged	0	1 (7.7)	0	0

Aspartate aminotransferase increased	0	0	1 (8.3)	0
Blood creatine phosphokinase MB increased	0	0	1 (8.3)	0
Blood iron decreased	0	1 (7.7)	0	0
Blood lead increased	0	0	1 (8.3)	0
Blood pressure diastolic increased	0	1 (7.7)	0	0
Cardiac murmur	0	1 (7.7)	0	0
Carnitine decreased	0	0	1 (8.3)	0
Crystal urine present	1 (33.3)	0	0	0
Electrocardiogram QT prolonged	0	1 (7.7)	0	0
Eosinophil count increased	0	1 (7.7)	0	0
Neutrophil count increased	0	0	1 (8.3)	0
Norovirus test positive	0	0	0	1 (25.0)
Respirovirus test positive	0	1 (7.7)	0	0
Metabolism and nutrition disorders	0	5 (38.5)	3 (25.0)	0
Weight gain poor	0	3 (23.1)	0	0
Dehydration	0	0	2 (16.7)	0
Decreased appetite	0	1 (7.7)	0	0
Feeding disorder	0	0	1 (8.3)	0
Malnutrition	0	1 (7.7)	0	0
Metabolic acidosis	0	0	1 (8.3)	0
Vitamin D deficiency	0	1 (7.7)	0	0
Musculoskeletal and connective tissue disorders	2	4 (30.8)	8 (66.7)	1 (25.0)
Scoliosis	0	0	4 (33.3)	0
Joint contracture	0	0	2 (16.7)	0
Kyphosis	0	2 (15.4)	0	0
Limb asymmetry	1 (33.3)	1 (7.7)	0	0
Pain in extremity	0	0	2 (16.7)	0

Arthralgia	0	0	1 (8.3)	0
Back pain	0	1 (7.7)	0	0
Joint stiffness	0	1 (7.7)	0	0
Knee deformity	1 (33.3)	0	0	0
Kyphoscoliosis	0	0	1 (8.3)	0
Mastication disorder	0	0	1 (8.3)	0
Muscle contracture	0	0	0	1 (25.0)
Muscle tightness	0	1 (7.7)	0	0
Soft tissue swelling	0	0	1 (8.3)	0
Tendinous contracture	0	0	1 (8.3)	0
Tendon discomfort	0	1 (7.7)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (8.3)	0
Acrochordon	0	0	1 (8.3)	0
Nervous system disorders	1 (33.3)	2 (15.4)	2 (16.7)	0
Headache	0	0	1 (8.3)	0
Language disorder	0	1 (7.7)	0	0
Migraine	0	0	1 (8.3)	0
Muscle contractions involuntary	0	1 (7.7)	0	0
Tremor	1 (33.3)	0	0	0
Psychiatric disorders	1 (33.3)	1 (7.7)	0	0
Irritability	0	1 (7.7)	0	0
Sleep terror	1 (33.3)	0	0	0
Reproductive system and breast disorders	0	0	0	1 (25.0)
Balanoposthitis	0	0	0	1 (25.0)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	6 (46.2)	9 (75.0)	2 (50.0)
Cough	0	3 (23.1)	7 (58.3)	1 (25.0)

Nasal congestion	1 (33.3)	2 (15.4)	2 (16.7)	0
Rhinorrhoea	0	2 (15.4)	2 (16.7)	1 (25.0)
Upper respiratory tract congestion	0	2 (15.4)	1 (8.3)	0
Respiration abnormal	0	1 (7.7)	1 (8.3)	0
Sleep apnoea syndrome	0	1 (7.7)	1 (8.3)	0
Atelectasis	0	0	1 (8.3)	0
Choking	0	0	1 (8.3)	0
Hypoxia	0	1 (7.7)	0	0
Respiratory tract congestion	0	1 (7.7)	0	0
Rhonchi	0	0	1 (8.3)	0
Skin and subcutaneous tissue disorders	2 (66.7)	8 (61.5)	6 (50.0)	1 (25.0)
Rash	1 (33.3)	2 (15.4)	3 (25.0)	0
Dermatitis diaper	1 (33.3)	2 (15.4)	0	1 (25.0)
Eczema	0	1 (7.7)	1 (8.3)	0
Erythema	0	1 (7.7)	1 (8.3)	0
Alopecia	0	1 (7.7)	0	0
Blister	0	1 (7.7)	0	0
Dermatitis contact	0	1 (7.7)	0	0
Dry skin	0	0	1 (8.3)	0
Hair growth abnormal	0	0	1 (8.3)	0
Papule	0	0	1 (8.3)	0
Perioral dermatitis	0	0	1 (8.3)	0
Skin irritation	0	0	1 (8.3)	0
Urticaria	0	0	1 (8.3)	0
Vascular disorders	1 (33.3)	4 (30.8)	1 (8.3)	0
Hypertension	0	3 (23.1)	0	0
Hypotension	1 (33.3)	0	1 (8.3)	0

Aortic dilatation	0	1 (7.7)	0	0
Flushing	0	1 (7.7)	0	0

IT = Intrathecal.

Conclusion:

- Participants 6 to <24 months of age at time of dosing: this age group did not meet the primary or secondary efficacy endpoints: the proportion of participants in Cohort 2 achieving the ability to stand alone (primary endpoint) was 7.7%, compared to 13.7% in the PNCR population. The proportion of participants achieving the ability to walk alone (secondary endpoint) was 7.7%, compared to 9.8% in the PNCR population. These results were not statistically significantly different.
- Participants 24 to <60 months of age at time of dosing:
    - The primary efficacy endpoint was met: the change from baseline in HFMSE score at Month 12 was statistically significantly different compared to the Primary PNCR population, with a LS mean difference of 5.5 (95% CI 1.9, 9.0) and a p-value of 0.0027 in favor of the AVXS-101-treated participants.
    - The secondary efficacy endpoint was not met: none of the participants in this age group achieved the ability to walk alone.

AVXS-101 administered IT was safe and well tolerated. Transaminase elevations (alanine transaminase/aspartate aminotransferase >3 x upper limit of normal) were noted in only one participant, without elevation of bilirubin. One participant had a confirmed low platelet value <75E9 that resolved spontaneously with no intervention. No participants had AEs indicative of cardiac toxicity (myocardial inflammation or thrombus), and no participants had AEs of thrombotic microangiopathy, or sensory abnormalities suggestive of ganglionitis.

Date of Clinical Study Report

04 Mar 2022