Clinical trial results:
Phase I, Open-Label, Dose Comparison Study of AVXS-101 for Sitting But Non-ambulatory Patients With Spinal Muscular Atrophy

Summary

EudraCT number	2020-003678-28
Trial protocol	Outside EU/EEA
Global end of trial date	18 November 2021

Results information

Result version number	v1
This version publication date	29 May 2022
First version publication date	29 May 2022

Trial information

Trial identification

Sponsor protocol code	AVXS-101-CL-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Gene Therapies EU Limited
Sponsor organisation address	2275 Half Day Road, Bannockburn, IL, United States, 60015
Public contact	EMEA Medical Information, Novartis Gene Therapies, Inc., +353 (1) 556-2364, medinfoemea.gtx@novartis.com
Scientific contact	EMEA Medical Information, Novartis Gene Therapies, Inc., +353 (1) 556-2364, medinfoemea.gtx@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002168-PIP01-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary safety objective was to assess the safety and tolerability of intrathecal 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 intrathecal injection. Safety and efficacy were assessed independently for each age cohort.

The primary efficacy objective, by age group was as follows:
- 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 [BSID] – 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).

Protection of trial subjects:

The study was conducted according to International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	32
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	20
Children (2-11 years)	12
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 32 participants took part in the trial at 11 sites in the United States between December 2017 and May 2021.

Pre-assignment

Screening details:

A total of 38 participants were screened, of which 6 were screen failures and 32 were enrolled and received study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: 6.0E13 Vector Genomes (vg) - Age 6 to <24 Months

Arm description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Arm type	Experimental
Investigational medicinal product name	AVXS-101
Investigational medicinal product code	
Other name	Onasemnogene abeparvovec
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

AVXS-101 was administered as an intrathecal injection at a dose of 6.0E13 vg.

Arm title	Cohort 2: 1.2E14 vg - Age 6 to <24 Months

Arm description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Arm type	Experimental
Investigational medicinal product name	AVXS-101
Investigational medicinal product code	
Other name	Onasemnogene abeparvovec
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

AVXS-101 was administered as an intrathecal injection at a dose of 1.2E14 vg.

Arm title	Cohort 2: 1.2E14 vg - Age 24 to <60 Months

Arm description:

Participants aged 24 to <60 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-

injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Arm type	Experimental
Investigational medicinal product name	AVXS-101
Investigational medicinal product code	
Other name	Onasemnogene abeparvovec
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

AVXS-101 was administered as an intrathecal injection at a dose of 1.2E14 vg.

Arm title	Cohort 3: 2.4E14 vg - Age 6 to <24 Months

Arm description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Arm type	Experimental
Investigational medicinal product name	AVXS-101
Investigational medicinal product code	
Other name	Onasemnogene abeparvovec
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

AVXS-101 was administered as an intrathecal injection at a dose of 2.4E14 vg.

Number of subjects in period 1	Cohort 1: 6.0E13 Vector Genomes (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
Started	3	13	12
Received AVXS-101	3	13	12
Completed	3	13	12

Number of subjects in period 1	Cohort 3: 2.4E14 vg - Age 6 to <24 Months
Started	4
Received AVXS-101	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: 6.0E13 Vector Genomes (vg) - Age 6 to <24 Months
Reporting group description:	
Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.	
Reporting group title	Cohort 2: 1.2E14 vg - Age 6 to <24 Months
Reporting group description:	
Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.	
Reporting group title	Cohort 2: 1.2E14 vg - Age 24 to <60 Months
Reporting group description:	
Participants aged 24 to <60 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.	
Reporting group title	Cohort 3: 2.4E14 vg - Age 6 to <24 Months
Reporting group description:	
Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.	

Reporting group values	Cohort 1: 6.0E13 Vector Genomes (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
Number of subjects	3	13	12
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	13	0
Children (2-11 years)	0	0	12
Age continuous Units: months			
arithmetic mean	17.2	16.7	37.5
standard deviation	± 4.1	± 4.5	± 10.6
Gender categorical Units: Subjects			
Female	2	6	6
Male	1	7	6
Ethnicity Units: Subjects			
Hispanic or Latino	2	3	0
Not Hispanic or Latino	1	10	12
Unknown or Not Reported	0	0	0

Race/Ethnicity Units: Subjects			
White	2	10	8
Asian	0	1	4
Other	0	1	0
Multiple	1	1	0

Reporting group values	Cohort 3: 2.4E14 vg - Age 6 to <24 Months	Total	
Number of subjects	4	32	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	4	20	
Children (2-11 years)	0	12	
Age continuous Units: months			
arithmetic mean	16.9		
standard deviation	± 5.6	-	
Gender categorical Units: Subjects			
Female	0	14	
Male	4	18	
Ethnicity Units: Subjects			
Hispanic or Latino	0	5	
Not Hispanic or Latino	4	27	
Unknown or Not Reported	0	0	
Race/Ethnicity Units: Subjects			
White	3	23	
Asian	1	6	
Other	0	1	
Multiple	0	2	

End points

End points reporting groups

Reporting group title	Cohort 1: 6.0E13 Vector Genomes (vg) - Age 6 to <24 Months

Reporting group description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 2: 1.2E14 vg - Age 6 to <24 Months

Reporting group description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 2: 1.2E14 vg - Age 24 to <60 Months

Reporting group description:

Participants aged 24 to <60 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 3: 2.4E14 vg - Age 6 to <24 Months

Reporting group description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Subject analysis set title	PNCR (Historical Control)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in historical control Pediatric Neuromuscular Clinical Research (PNCR) cohort received uniform standard of care treatment. Participants visited the study site at baseline and at 2, 4, 6, 9, 12 months and every 6 months thereafter.

Primary: Age 6 to <24 Months Only: Number of Participants Who Achieved the Ability to Stand Alone

End point title	Age 6 to <24 Months Only: Number of Participants Who Achieved the Ability to Stand Alone[1][2]

End point description:

Defined by the BSID GM subtest performance criteria number 40, confirmed by video recording, as a participant who stands alone for at least 3 seconds unsupported. Intent-to-Treat (ITT) Set which included all enrolled participants who were given an AVXS-101 intrathecal injection. Participants were analyzed according to the assigned dose.

End point type	Primary

End point timeframe:

From Day 1 up to Month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Pre-specified comparative statistical analysis is reported in the applicable 'Other pre-specified' endpoint.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were only planned to be collected for participants aged 6 to <24 months.

End point values	Cohort 1: 6.0E13 Vector Genomes (vg) - Age 6 to <24 Months	Cohort 2: 1.2E14 vg - Age 6 to <24 Months	Cohort 3: 2.4E14 vg - Age 6 to <24 Months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	13	4	
Units: participants				
Able to Stand Alone	1	1	0	
Unable to Stand Alone	2	12	4	

Statistical analyses

No statistical analyses for this end point

Primary: Age 24 to <60 Months Only: Change from Baseline in HFMSE Score at Month 12

End point title	Age 24 to <60 Months Only: Change from Baseline in HFMSE Score at Month 12[3][4]

End point description:

The HFMSE contained 33 items which were scored on a scale of 0-2 with a total achievable score ranging from 0, if all activities are failed, to 66, if all the activities are achieved. A positive change from baseline indicates a better outcome. ITT Set which included all enrolled participants who were given an AVXS-101 intrathecal injection. Participants were analyzed according to the assigned dose.

End point type	Primary

End point timeframe:

Baseline and Month 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Pre-specified comparative statistical analysis is reported in the applicable 'Other pre-specified' endpoint.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were only planned to be collected for participants aged 24 to <60 months.

End point values	Cohort 2: 1.2E14 vg - Age 24 to <60 Months			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: score on a scale				
least squares mean (confidence interval 95%)	6.0 (3.7 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)[5]

End point description:

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.

Evaluation of TEAEs included the number of participants with at least one:
• TEAE
• Serious TEAE
• TEAE related to AVXS-101
• TEAE with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 (grade 3 = severe or medically significant to grade 5 = death related to TEAE)

Safety Analysis Set which included all participants given an AVXS-101 intrathecal injection. Participants were analyzed according to actual dose received.

End point type	Primary

End point timeframe:

Adverse events were collected from the single dose of study treatment until 12 months for Cohorts 1 and 2 and 15 months for Cohort 3

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparative statistical analysis was planned for this endpoint.

End point values	Cohort 1: 6.0E13 Vector Genomes (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
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	12	4
Units: participants				
TEAE	3	13	12	4
Serious TEAE	1	2	4	0
TEAE Related to AVXS-101	0	7	4	1
TEAE with CTCAE Grade ≥ 3	1	4	4	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved the Ability to Walk Alone

End point title	Number of Participants Who Achieved the Ability to Walk Alone

End point description:

Defined by the BSID GM subtest performance criteria number 43, confirmed by video recording, as a participant who takes 5 coordinated independent steps. ITT Set which included all enrolled participants who were given an AVXS-101 intrathecal injection. Participants were analyzed according to the assigned dose.

End point type	Secondary

End point timeframe:

From Day 1 up to Month 12

End point values	Cohort 1: 6.0E13 Vector Genomes (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
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	12	4
Units: participants				
Able to Walk Alone	0	1	0	0
Unable to Walk Alone	3	12	12	4

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of Hours Per Day of Non-invasive Ventilatory Support

End point title	Average Number of Hours Per Day of Non-invasive Ventilatory Support

End point description:

Participants were assessed by a pulmonologist and may have been fitted with a non-invasive positive pressure ventilatory (e.g., Bilevel Positive Airway Pressure BiPAP) at the discretion of the pulmonologist and/or investigator. The number of hours per day of non-invasive ventilatory support was captured continuously by the device. Data were only collected in participants requiring BiPAP support. 99999 = no data are available. 9999 = Only 1 participant had available data so standard deviation could not be calculated.

End point type	Secondary

End point timeframe:

Months 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

End point values	Cohort 1: 6.0E13 Vector Genomes (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
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	1[7]	1	0[8]
Units: hours/day				
arithmetic mean (standard deviation)				
Month 2	()	99999 (± 9999)	10.530 (± 9999)	()
Month 3	()	99999 (± 9999)	2.930 (± 9999)	()
Month 4	()	0.000 (± 9999)	5.860 (± 9999)	()
Month 5	()	0.000 (± 9999)	4.610 (± 9999)	()
Month 6	()	2.590 (± 9999)	4.490 (± 9999)	()
Month 7	()	4.550 (± 9999)	7.490 (± 9999)	()
Month 8	()	7.170 (± 9999)	8.290 (± 9999)	()
Month 9	()	8.690 (± 9999)	7.690 (± 9999)	()
Month 10	()	10.320 (± 9999)	9.900 (± 9999)	()
Month 11	()	14.050 (± 9999)	3.460 (± 9999)	()

Month 12	()	10.120 (± 9999)	0.040 (± 9999)	()

Notes:

[6] - No participants required BiPAP support in this arm.

[7] - Months 2 and 3 N = 0

[8] - No participants required BiPAP support in this arm.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Age 6 to <24 Months Only: Number of Participants Who Achieved the Ability to Stand Alone Versus the Population-matched Natural History Pediatric Neuromuscular Clinical Research Network (PNCR) Control Study

End point title	Age 6 to <24 Months Only: Number of Participants Who Achieved the Ability to Stand Alone Versus the Population-matched Natural History Pediatric Neuromuscular Clinical Research Network (PNCR) Control Study[9]

End point description:

Defined by the BSID GM subtest performance criteria number 40, confirmed by video recording, as a participant who stands alone for at least 3 seconds unsupported. ITT Set which included all enrolled participants who were given an AVXS-101 intrathecal injection. Participants were analyzed according to the assigned dose. The PNCR population included all participants with 3 copies of survival of motor neuron 2 (SMN2) with biallelic survival or motor neuron 1 (SMN1) mutations, symptom onset <12 months of age, diagnosis <24 months of age, no standing, no walking, and assessments at ≥24 months and <60 months of age (baseline).

End point type	Other pre-specified

End point timeframe:

From Day 1 up to Month 12

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were only planned to be collected for participants aged 6 to <24 months.

End point values	Cohort 1: 6.0E13 Vector Genomes (vg) - Age 6 to <24 Months	Cohort 2: 1.2E14 vg - Age 6 to <24 Months	Cohort 3: 2.4E14 vg - Age 6 to <24 Months	PNCR (Historical Control)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	13	4	51
Units: participants				
Able to Stand Alone	1	1	0	7
Unable to Stand Alone	2	12	4	44

Statistical analyses

Statistical analysis title	Cohort 2: 1.2E14 vg - Age 6 to <24 Months vs PNCR

Statistical analysis description:

Difference in the percentage of participants who achieved the ability to stand alone.

Comparison groups	Cohort 2: 1.2E14 vg - Age 6 to <24 Months v PNCR (Historical Control)

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.9999
Method	Fisher exact
Parameter estimate	Difference in Percent
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.8
upper limit	22.8

Other pre-specified: Age 24 to <60 Months Only: Change from Baseline in HFMSE Score Versus the Population-matched Natural History PNCR Control Study at Month 12

End point title	Age 24 to <60 Months Only: Change from Baseline in HFMSE Score Versus the Population-matched Natural History PNCR Control Study at Month 12[10]

End point description:

The HFMSE contained 33 items which were scored on a scale of 0-2 with a total achievable score ranging from 0, if all activities are failed, to 66, if all the activities are achieved. A positive change from baseline indicates a better outcome. ITT Set which included all enrolled participants who were given an AVXS-101 intrathecal injection. Participants were analyzed according to the assigned dose. The PNCR population included all participants who met the criteria of having 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 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.

End point type	Other pre-specified

End point timeframe:

Baseline and Month 12

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were only planned to be collected for participants aged 24 to <60 months.

End point values	Cohort 2: 1.2E14 vg - Age 24 to <60 Months	PNCR (Historical Control)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	9		
Units: score on a scale				
least squares mean (confidence interval 95%)	6.0 (3.7 to 8.3)	0.5 (-2.2 to 3.2)		

Statistical analyses

Statistical analysis title	Cohort 2: 1.2E14 vg - Age 24 to <60 Months vs PNCR
Comparison groups	Cohort 2: 1.2E14 vg - Age 24 to <60 Months v PNCR (Historical Control)
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027
Method	Mixed-Model Repeat Measure
Parameter estimate	Difference between Least Squares Mean
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	9

Other pre-specified: Number of Participants Who Achieved the Ability to Walk Alone Versus the Population-matched Natural History PNCR Control Study

End point title	Number of Participants Who Achieved the Ability to Walk Alone Versus the Population-matched Natural History PNCR Control Study

End point description:

Defined by the BSID GM subtest performance criteria number 43, confirmed by video recording, as a participant who takes 5 coordinated independent steps. ITT Set which included all enrolled participants who were given an AVXS-101 intrathecal injection. Participants were analyzed according to the assigned dose. The PNCR population included all participants with 3 copies of SMN2 with biallelic SMN1 mutations, symptom onset <12 months of age, diagnosis <24 months of age, no standing, no walking, and assessments at ≥24 months and <60 months of age (baseline).

End point type	Other pre-specified

End point timeframe:

From Day 1 up to Month 12

End point values	Cohort 1: 6.0E13 Vector Genomes (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
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	12	4
Units: participants				
Able to Walk Alone	0	1	0	0
Unable to Walk Alone	3	12	12	4

End point values	PNCR (Historical Control)			

Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: participants				
Able to Walk Alone	5			
Unable to Walk Alone	46			

Statistical analyses

Statistical analysis title	Cohort 2: 1.2E14 vg - Age 6 to <24 Months vs PNCR
Statistical analysis description:	
Difference in the percentage of participants who achieved the ability to walk alone.	
Comparison groups	Cohort 2: 1.2E14 vg - Age 6 to <24 Months v PNCR (Historical Control)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.9999
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	27

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the single dose of study treatment until 12 months for Cohorts 1 and 2 and 15 months for Cohort 3

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Cohort 1: 6.0E13 Vector Genomes (vg) - Age 6 to <24 Months

Reporting group description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 2: 1.2E14 vg - Age 6 to <24 Months

Reporting group description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 2: 1.2E14 vg - Age 24 to <60 Months

Reporting group description:

Participants aged 24 to <60 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Reporting group title	Cohort 3: 2.4E14 vg - Age 6 to <24 Months

Reporting group description:

Participants aged 6 to <24 months at time of AVXS-101 dosing received a single dose of AVXS-101 on Day 1 of the overall study. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1 mg/kg/day from 1 day prior to AVXS-101 injection until at least 30 days post-injection at which point the prednisolone dose could be tapered downwards. At week 9, prednisolone could be discontinued.

Serious adverse events	Cohort 1: 6.0E13 Vector Genomes (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
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	4 / 12 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3: 2.4E14 vg - Age 6 to <24 Months		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1: 6.0E13 Vector Genomes (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
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	13 / 13 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Aortic dilatation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	3 / 3 (100.00%)	6 / 13 (46.15%)	7 / 12 (58.33%)
occurrences (all)	3	9	8
Application site irritation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infusion site bruising			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	7 / 12 (58.33%)
occurrences (all)	0	5	15
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	2 / 12 (16.67%)
occurrences (all)	1	2	4
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Upper respiratory tract congestion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Respiration abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Sleep apnoea syndrome			

subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Choking			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rhonchi			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sleep terror			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood creatine phosphokinase MB increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood iron decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood lead increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood pressure diastolic increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Carnitine decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Crystal urine present			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eosinophil count increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Neutrophil count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Norovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respirovirus test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural			

complications			
Arthropod bite			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Skin abrasion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Pectus carinatum			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pectus excavatum			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Mitral valve incompetence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Cardiomegaly			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Pulmonary valve incompetence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Language disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle contractions involuntary			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Motion sickness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	5 / 13 (38.46%)	3 / 12 (25.00%)
occurrences (all)	0	11	5

Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	3 / 12 (25.00%)
occurrences (all)	0	2	5
Teething			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Anal fissure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tooth resorption			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	3 / 12 (25.00%)
occurrences (all)	1	2	4
Dermatitis diaper			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hair growth abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Perioral dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	0	4
Joint contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Kyphosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Limb asymmetry			
subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Joint stiffness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Knee deformity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Kyphoscoliosis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mastication disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Soft tissue swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tendinous contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tendon discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 3 (66.67%)	10 / 13 (76.92%)	5 / 12 (41.67%)
occurrences (all)	3	22	12
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	2 / 12 (16.67%)
occurrences (all)	0	4	3
Otitis media			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	3 / 12 (25.00%)
occurrences (all)	2	0	3
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0

Ear infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Bacteriuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Coxsackie viral infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Furuncle			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Metapneumovirus infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Respiratory tract infection viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rhinovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Viral pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Viral rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Weight gain poor			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Feeding disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Malnutrition			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolic acidosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vitamin D deficiency			

subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort 3: 2.4E14 vg - Age 6 to <24 Months		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Aortic dilatation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Application site irritation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infusion site bruising			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiration abnormal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Atelectasis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Choking			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypoxia			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhonchi			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sleep terror			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood iron decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood lead increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood pressure diastolic increased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Carnitine decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Crystal urine present			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eosinophil count increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neutrophil count increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Norovirus test positive			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respirovirus test positive			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin abrasion			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Pectus carinatum			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pectus excavatum			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mitral valve incompetence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiomegaly			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pericardial effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pulmonary valve incompetence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Language disorder			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Migraine			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Muscle contractions involuntary			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Motion sickness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Teething			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Abdominal pain			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tooth resorption			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dermatitis diaper			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eczema			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blister			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hair growth abnormal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Papule			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Perioral dermatitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin irritation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Joint contracture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Kyphosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Limb asymmetry			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Joint stiffness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Knee deformity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Kyphoscoliosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mastication disorder			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Muscle contracture			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Muscle tightness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Soft tissue swelling			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tendinous contracture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tendon discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Bacteriuria				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Coxsackie viral infection				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Croup infectious				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Furuncle				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Gastroenteritis viral				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Metapneumovirus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Parainfluenzae virus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Respiratory tract infection viral				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rhinovirus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			

Viral pharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Viral rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Metabolism and nutrition disorders Weight gain poor subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Dehydration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Decreased appetite subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Feeding disorder subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Malnutrition subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Metabolic acidosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2016	The following updates were made: • Study design, inclusion/exclusion criteria, safety criteria for discontinuation, and schedule of assessment were updated.
17 February 2017	The following updates were made: • Study was re-designed as open-label-label, with a broader age range of participants • Multiple revisions to reflect change to open-label study design • Specify non-ambulatory participants • Revised primary, secondary, and exploratory objectives • 1-year follow up instead of 2 years • Added nusinersen information to Background • Revisions to study drug packaging, labeling, storage, preparation, administration, accountability, handling and disposal • Clarification for assessment of motor milestones • Revisions to sample size calculation, and primary, secondary, and additional efficacy endpoints
29 March 2017	The following updates were made: • Clarified age requirements and expectation for respiratory syncytial virus vaccination • Excluded participants with gene mutations rather than homozygous deletions • Increased dose
11 December 2017	The following updates were made: • Specified lower age requirement for the lower age cohort and monitoring of the cardiac enzyme creatine kinase-MB (CK-MB) • Allowed for high altitude pulse oximetry measurements • Defined Intent-to-Treat and Enrolled sets
18 October 2018	The following updates were made: • Added Dose C and additional changes to reflect dose escalation and study design • Increased number of participants enrolled based on addition of Dose C • Added minimum age requirement for the lower age cohort • Included monitoring of cardiac enzyme CK-MB and Troponin I, and added additional cardiac monitoring • Updated Good Laboratory Practices (GLP) toxicology data • Minor clarifications to Schedule of Assessments • Added measurement of head circumference
17 June 2019	The following updates were made: • Added more stringent eligibility criteria for liver function tests and additional visits for monitoring liver function, following an acute liver failure case reported in the US Managed Access Program • Added benefit/risk language, information on liver failure case, and description of recent adverse events • Added liver function criteria to prednisolone taper and discontinuation • Added completed first-in-human trial data • Revised and reorganized Schedule of Assessments; added Day 44 and Day 72 visits and further clarification on data monitoring committee (DMC) scheduling • Updated participant withdrawal and discontinuation criteria • Added a supportive efficacy analysis

26 February 2020	This amendment was finalized during the partial clinical hold and submitted to the Food and Drug Administration (FDA) but not to local institutional review boards (IRBs), and the amendment was not implemented by the investigator sites. The following updates were made: ● Updates to facilitate detection of clinical symptoms and signs suggestive of ganglionopathy. ● The introduction of the age-appropriate sensory testing as part of the neurological examination, had been implemented for ongoing participants, via an Urgent Safety Measure on 25-Oct-2019. The addition of Sensory Nerve Action Potential (SNAP) at Screening, Day 30 and Month 6, and assessment of neopterin levels at every visit was to apply only to new participants, of which none were enrolled under this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported