Clinical trial results:
Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy

Summary

EudraCT number	2019-002663-10
Trial protocol	LV IE HU PL ES GB DE FR GR IT NL
Global end of trial date	30 May 2024

Results information

Result version number	v2 (current)
This version publication date	12 July 2025
First version publication date	13 December 2024
Version creation reason	• Correction of full data set Updates were made to a primary endpoint and several secondary endpoints to align the results with the CT.gov.

Trial information

Trial identification

Sponsor protocol code	232SM203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04089566
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, Massachusetts, United States, 02142
Public contact	Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	30 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with spinal muscular atrophy (SMA), as measured by change in Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score (Part B); to examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA (Parts A and C).

Protection of trial subjects:

Written informed consent was obtained from each subject’s parent or legal guardian prior to evaluations being performed for eligibility. Adequate time to review the information in the informed consent and ask questions concerning all portions of the conduct of the study was provided. Through the informed consent process, awareness of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken was made. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Saudi Arabia: 15
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 8

Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Hungary: 2
Worldwide total number of subjects	145
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	4
Infants and toddlers (28 days-23 months)	71
Children (2-11 years)	39
Adolescents (12-17 years)	7
Adults (18-64 years)	23
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part at the investigative sites in the United States, Brazil, Canada, Chile, China, Colombia, Estonia, Germany, Hungary, Italy, Japan, Lebanon, Mexico, Poland, Russia, Saudi Arabia, Spain, and Taiwan from 26 March 2020 to 30 May 2024.

Pre-assignment

Screening details:

A total of 145 participants diagnosed with spinal muscular atrophy (SMA) were enrolled in the 3-parts (Parts A, B, and C). Of which, 117 of participants completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: 28/28 Milligrams (mg) Nusinersen

Arm description:

Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.

Arm type	Experimental
Investigational medicinal product name	Nusinersen
Investigational medicinal product code	BIIB058
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen

Arm description:

Participants with infantile-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

Arm type	Experimental
Investigational medicinal product name	Nusinersen
Investigational medicinal product code	BIIB058
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen

Arm description:

Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

Arm type	Experimental

Investigational medicinal product name	Nusinersen
Investigational medicinal product code	BIIB058
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part B: Later-Onset SMA: 12/12 mg Nusinersen

Arm description:

Participants with later-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

Arm type	Experimental
Investigational medicinal product name	Nusinersen
Investigational medicinal product code	BIIB058
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part B: Later-Onset SMA: 50/28 mg Nusinersen

Arm description:

Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

Arm type	Experimental
Investigational medicinal product name	Nusinersen
Investigational medicinal product code	BIIB058
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part C: 50/28 mg Nusinersen

Arm description:

Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.

Arm type	Experimental
Investigational medicinal product name	Nusinersen
Investigational medicinal product code	BIIB058
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Started	6	25	50
Completed	6	13	35
Not completed	0	12	15
Adverse event, serious fatal	-	6	10
Withdrawal by Parent or Guardian	-	2	1
Reason not Specified	-	4	4

Number of subjects in period 1	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen
Started	8	16	40
Completed	7	16	40
Not completed	1	0	0
Adverse event, serious fatal	-	-	-
Withdrawal by Parent or Guardian	-	-	-
Reason not Specified	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: 28/28 Milligrams (mg) Nusinersen
Reporting group description:	
Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.	
Reporting group title	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen
Reporting group description:	
Participants with infantile-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.	
Reporting group title	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Reporting group description:	
Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.	
Reporting group title	Part B: Later-Onset SMA: 12/12 mg Nusinersen
Reporting group description:	
Participants with later-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.	
Reporting group title	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Reporting group description:	
Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.	
Reporting group title	Part C: 50/28 mg Nusinersen
Reporting group description:	
Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.	

Reporting group values	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Number of subjects	6	25	50
Age categorical Units: participants			
In Utero	0	0	0
Preterm newborn infants (gestational age<37 wks)	0	0	0
Newborns (0-27 days)	0	1	3
Infants and toddlers (28 days - 23 months)	0	24	47
Children (2 - 11 years)	5	0	0
Adolescents (12 - 17 years)	1	0	0
Adults (18 - 64 years)	0	0	0
From 65 - 84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: participants			
Male	5	14	26

Female	1	11	24

Race Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	2	4	10
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	4	17	29
Not Reported Due to Confidentiality Regulations	0	0	2
Other	0	4	7
Multiple	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	10	18
Not Hispanic or Latino	5	13	30
Not reported	0	2	2

Reporting group values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen
Number of subjects	8	16	40
Age categorical Units: participants			
In Utero	0	0	0
Preterm newborn infants (gestational age<37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	8	16	10
Adolescents (12 - 17 years)	0	0	6
Adults (18 - 64 years)	0	0	23
From 65 - 84 years	0	0	1
85 years and over	0	0	0
Gender categorical Units: participants			
Male	2	2	25
Female	6	14	15
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	5	7
Black or African American	0	1	0
Native Hawaiian or other Pacific Islander	0	0	0
White	3	8	32
Not Reported Due to Confidentiality Regulations	0	0	0
Other	3	2	1
Multiple	0	0	0

Ethnicity Units: Subjects			
Hispanic or Latino	2	6	5
Not Hispanic or Latino	6	10	35
Not reported	0	0	0

Reporting group values	Total		
Number of subjects	145		
Age categorical Units: participants			
In Utero	0		
Preterm newborn infants (gestational age<37 wks)	0		
Newborns (0-27 days)	4		
Infants and toddlers (28 days - 23 months)	71		
Children (2 - 11 years)	39		
Adolescents (12 - 17 years)	7		
Adults (18 - 64 years)	23		
From 65 - 84 years	1		
85 years and over	0		
Gender categorical Units: participants			
Male	74		
Female	71		
Race Units: Subjects			
American Indian or Alaska Native	2		
Asian	30		
Black or African American	1		
Native Hawaiian or other Pacific Islander	0		
White	93		
Not Reported Due to Confidentiality Regulations	2		
Other	17		
Multiple	0		
Ethnicity Units: Subjects			
Hispanic or Latino	42		
Not Hispanic or Latino	99		
Not reported	4		

Subject analysis sets

Subject analysis set title	CS3B Matched Sham Control Group
Subject analysis set type	Full analysis

Subject analysis set description:

Historical data of participants who received sham treatment, IT, on Days 1, 15, 29, 64, 183, and 302 in the double-blind, phase 3 study CS3B (2013-004422-29), was used as control in the current study.

Reporting group values	CS3B Matched Sham Control Group		
Number of subjects	20		
Age categorical Units: participants			
In Utero	0		
Preterm newborn infants (gestational age<37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days - 23 months)	0		
Children (2 - 11 years)	0		
Adolescents (12 - 17 years)	0		
Adults (18 - 64 years)	0		
From 65 - 84 years	0		
85 years and over	0		
Gender categorical Units: participants			
Male	0		
Female	0		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Black or African American	0		
Native Hawaiian or other Pacific Islander	0		
White	0		
Not Reported Due to Confidentiality Regulations	0		
Other	0		
Multiple	0		
Ethnicity Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	0		
Not reported	0		

End points

End points reporting groups

Reporting group title	Part A: 28/28 Milligrams (mg) Nusinersen

Reporting group description:

Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.

Reporting group title	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen

Reporting group description:

Participants with infantile-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

Reporting group title	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen

Reporting group description:

Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

Reporting group title	Part B: Later-Onset SMA: 12/12 mg Nusinersen

Reporting group description:

Participants with later-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

Reporting group title	Part B: Later-Onset SMA: 50/28 mg Nusinersen

Reporting group description:

Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

Reporting group title	Part C: 50/28 mg Nusinersen

Reporting group description:

Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.

Subject analysis set title	CS3B Matched Sham Control Group
Subject analysis set type	Full analysis

Subject analysis set description:

Historical data of participants who received sham treatment, IT, on Days 1, 15, 29, 64, 183, and 302 in the double-blind, phase 3 study CS3B (2013-004422-29), was used as control in the current study.

Primary: Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

End point title	Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group[1]

End point description:

The CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. It included 16 items (capturing neck, trunk, and proximal and distal limb strength), nine of which were scored 0, 1, 2, 3, or 4, five were scored as 0, 2, or 4, one was scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4 with greater scores indicating greater muscle strength. Total score ranged from 0 (worst possible score) and 64 (best possible score). The change from baseline to Day 183 in the CHOP-INTEND total score was compared to CS3B study (2013-004422-29) sham control group using the joint-rank methodology to account for mortality. As stated in protocol a matched sham set was defined for the analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set.

End point type	Primary

End point timeframe:

Baseline, Day 183

Notes:

[1] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	CS3B Matched Sham Control Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	20		
Units: score on scale				
least squares mean (confidence interval 95%)	42.9 (38.7 to 47.2)	16.9 (10.1 to 23.7)		

Statistical analyses

Statistical analysis title	Change From Baseline in CHOP-INTEND Total Score
Comparison groups	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen v CS3B Matched Sham Control Group
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	26.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.941
upper limit	34.172
Variability estimate	Standard error of the mean
Dispersion value	4.141

Notes:

[2] - The Analysis of Covariance (ANCOVA) model used rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

Primary: Parts A and C: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (TESAEs)

End point title	Parts A and C: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (TESAEs)[3][4]

End point description:

An adverse event (AE):any unfavorable & unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with use of an investigational product, whether or not related to investigational product. SAE:any untoward medical occurrence that at any dose resulted in death, in view of Investigator, placed participant at immediate risk of death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a birth defect. AE and SAEs were regarded as treatment-emergent if it was present prior to receiving first dose of nusinersen in current study and subsequently worsened in severity or was not present prior to receiving first dose of nusinersen and subsequently

appeared Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study.

End point type	Primary

End point timeframe:

Part A: From the first dose of the study drug up to Day 389, Part C: From the first dose of the study drug up to Day 361

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: Only descriptive statistics were planned for this 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
TEAEs	4	37		
TESAEs	1	6		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)

End point title	Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)[5][6]

End point description:

Blood chemistry parameters included protein, albumin, creatinine, blood urea nitrogen, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, and creatine kinase. Parameters were flagged as low, normal/ high relative to normal range/ as unknown if no result was available, by Investigator. Here, shift to low indicates values that were normal, high/ unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. Categories with at least one participant with shift from baseline are reported. Part A: safety analysis set. Part C: ITT set. Safety and ITT set included all participants who received at least one dose of nusinersen. Number analyzed 'n' is number of participants evaluable for analysis of the specified parameter.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

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: Only descriptive statistics were planned for this endpoint.

[6] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Alkaline Phosphatase Shift to High (n=6,39)	1	2		
Alanine Aminotransferase Shift to High(n=6,34)	0	6		
Aspartate Aminotransferase Shift to High (n=6,37)	0	8		
Bicarbonate Shift to Low (n=2,31)	1	6		
Bicarbonate Shift to High (n=2,40)	0	2		
Bilirubin Shift to High (n=6,40)	0	1		
Indirect Bilirubin Shift to Low (n=4,26)	4	12		
Indirect Bilirubin Shift to High (n=6,40)	0	1		
Calcium Shift to High (n=6,39)	0	1		
Creatine Kinase Shift to Low (n=6,39)	0	0		
Creatine Kinase Shift to High (n=3,22)	0	1		
Chloride Shift to Low (n=6,40)	0	1		
Creatinine Shift to Low (n=1,2)	0	1		
Glucose Shift to Low (n=6,37)	0	3		
Glucose Shift to High (n=5,33)	3	9		
Potassium Shift to High (n=6,39)	1	1		
Phosphate Shift to High (n=5,36)	2	10		
Sodium Shift to High (n=6,40)	0	1		
Urea Nitrogen Shift to Low (n=6,39)	0	1		
Urea Nitrogen Shift to High (n=6,39)	1	3		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Hematology Parameters)

End point title	Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Hematology Parameters)[7][8]

End point description:

Hematology parameters included complete blood cell count, with dierential and platelet count, and absolute neutrophil count. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Number analysed (n)' indicates the number of participants evaluable for the specified hematology parameter.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[7] - 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: Only descriptive statistics were planned for this endpoint.

[8] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Basophils Shift to High (n=3,37)	2	6		
Basophils/Leukocytes Shift to High(n=2,35)	2	6		
Eosinophils Shift to High(n=5,39)	1	3		
Eosinophils/Leukocytes Shift to High(n=4,36)	3	9		
Hematocrit Shift to Low(n=5,40)	0	2		
Hematocrit Shift to High(n=6,40)	1	0		
Hemoglobin Shift to Low(n=6,40)	0	3		
Lymphocytes Shift to High(n=5,39)	0	1		
Lymphocytes/Leukocytes Shift to Low(n=6,39)	0	2		
Lymphocytes/Leukocytes Shift to High(n=6,36)	0	3		
Monocytes Shift to Low(n=4,39)	1	4		
Monocytes/Leukocytes Shift to Low(n=4,35)	3	2		
Monocytes/Leukocytes Shift to High(n=6,40)	0	2		
Neutrophils Shift to Low(n=6,35)	0	5		
Neutrophils Shift to High(n=6,40)	0	2		
Neutrophils/Leukocytes Shift to Low (n=5,38)	1	4		
Neutrophils/Leukocytes Shift to High(n=6,39)	0	2		
Platelets Shift to Low(n=6,39)	0	1		
Platelets Shift to High(n=6,40)	0	1		
Leukocytes Shift to Low(n=6,36)	0	3		
Leukocytes Shift to High(n=6,40)	0	3		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Urinalysis Parameters)

End point title	Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Urinalysis Parameters)[9][10]

End point description:

Urinalysis included assessments of urine total protein, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts and crystals. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Number analysed (n)' indicates the number of participants evaluable for the specified urinalysis parameter.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[9] - 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: Only descriptive statistics were planned for this endpoint.

[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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Specific Gravity Shift to High (n=5,40)	2	1		
pH Shift to High (n=6,40)	0	2		
Protein High/positive (n=5,38)	4	9		
Glucose High/positive (n=6,40)	0	2		
Ketones High/positive (n=5,36)	1	8		
Occult Blood High/positive (n=6,38)	2	4		
RBC High/positive (n=4,12)	1	1		
WBC High/positive (n=2,23)	0	2		
Epithelial Cells High/positive (n=1,4)	0	4		
Bacteria High/positive (n=1,2)	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Cerebrospinal Fluid (CSF) Parameters

End point title	Parts A and C: Number of Participants With Shifts From Baseline in Cerebrospinal Fluid (CSF) Parameters[11][12]

End point description:

CSF parameters included cell count, total protein, and glucose. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at

baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Number analysed (n)' indicates the number of participants evaluable for the specified urinalysis parameter.

End point type	Primary

End point timeframe:

Parts A: Baseline up to Day 269 Parts C: Baseline up to Day 241

Notes:

[11] - 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: Only descriptive statistics were planned for this endpoint.

[12] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Glucose Shift to Low (n=5,38)	1	2		
Glucose Shift to High (n=6,38)	0	2		
Protein Shift to Low (n=6,39)	0	3		
Protein Shift to High (n=6,37)	0	8		
Erythrocytes Shift to High (n=5,34)	2	8		
Leukocytes Shift to High (n=5,36)	1	6		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Electrocardiograms (ECGs)

End point title	Parts A and C: Number of Participants With Shifts From Baseline in Electrocardiograms (ECGs)[13][14]

End point description:

The ECGs were assessed by the investigator to be normal, abnormal and abnormal AE. The number of participants with ECG shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) was assessed. Shift from baseline to worst post-baseline values were reported. The categories with at least one participant with shift from baseline in ECG are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[13] - 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: Only descriptive statistics were planned for this endpoint.

[14] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Normal to Normal	0	10		
Normal to Abnormal, not AE	3	12		
Abnormal, not AE to Abnormal, not AE	3	17		
Unknown to Abnormal, not AE	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Abnormalities in Vital Sign Parameters

End point title	Parts A and C: Number of Participants With Abnormalities in Vital Sign Parameters [15][16]

End point description:

Vital sign assessment included temperature, pulse rate systolic blood pressure, diastolic blood pressure, and respiratory rate. As pre-specified in protocol, the criteria for determining potentially clinically relevant abnormalities in vital signs included: temperature < 36 and > 38 degrees Celsius (C), pulse rate < 60 and > 100 beats per minute (bpm), systolic blood pressure [< 90, > 140 and > 160 millimeters of mercury (mmHg)], diastolic blood pressure < 50, > 90 and > 100 mmHg and respiratory rate < 12 and > 20 breaths per minute. The categories with at least one participant with clinically relevant vital sign abnormalities are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[15] - 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: Only descriptive statistics were planned for this endpoint.

[16] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Temperature <36.0 C	4	13		
Pulse rate <60 bpm	1	14		

Pulse rate >100 bpm	6	19		
Systolic blood pressure <90 mmHg	4	13		
Systolic blood pressure >140 mmHg	0	3		
Diastolic blood pressure <50 mmHg	3	10		
Diastolic blood pressure >90 mmHg	1	7		
Respiratory rate <12 breaths/min	0	1		
Respiratory rate >20 breaths/min	6	27		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Change From Baseline in Growth Parameters (Ulnar Length)

End point title	Parts A and C: Change From Baseline in Growth Parameters (Ulnar Length)[17][18]

End point description:

As pre-specified in the protocol, ulnar length was measured for participants with later-onset SMA. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[17] - 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: Only descriptive statistics were planned for this endpoint.

[18] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	27		
Units: cm				
arithmetic mean (standard deviation)	1.8 (± 1.43)	0.0 (± 1.27)		

Statistical analyses

No statistical analyses for this end point

Primary: Part C: Change From Baseline in Growth Parameters (Arm Circumference)

End point title	Part C: Change From Baseline in Growth Parameters (Arm Circumference)[19][20]

End point description:

As pre-specified in the protocol, arm circumference was measured for participants with infantile-onset

SMA. ‘99999’ signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. ITT set included all participants who received at least one dose of nusinersen in the current study. ‘Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Baseline, Day 302

Notes:

[19] - 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: Only descriptive statistics were planned for this endpoint.

[20] - 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: Part C arm was planned to be analysed for this end point.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: cm				
arithmetic mean (standard deviation)	-1.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Part C: Change From Baseline in Growth Parameters (Chest Circumference)

End point title	Part C: Change From Baseline in Growth Parameters (Chest Circumference)[21][22]

End point description:

As pre-specified in protocol, chest circumference was measured for participants with infantile-onset SMA only. ‘99999’ signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. ITT set included all participants who received at least one dose of nusinersen in the current study. ‘Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Baseline, Day 302

Notes:

[21] - 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: Only descriptive statistics were planned for this endpoint.

[22] - 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: Part C arm was planned to be analysed for this end point.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: cm				
arithmetic mean (standard deviation)	2.5 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Part C: Change From Baseline in Growth Parameters (Head Circumference)

End point title	Part C: Change From Baseline in Growth Parameters (Head Circumference)[23][24]

End point description:

As pre-specified in the protocol, head circumference was measured for participants with infantile-onset SMA only. ITT set included all participants who received at least one a dose of nusinersen in the current study. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Baseline, Day 302

Notes:

[23] - 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: Only descriptive statistics were planned for this endpoint.

[24] - 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: Part C arm was planned to be analysed for this end point.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: cm				
arithmetic mean (standard deviation)	2.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Change From Baseline in Growth Parameters (Body Height)

End point title	Parts A and C: Change From Baseline in Growth Parameters (Body Height)[25][26]

End point description:

Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[25] - 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: Only descriptive statistics were planned for this endpoint.

[26] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	32		
Units: centimeters (cm)				
arithmetic mean (standard deviation)	7.2 (± 1.70)	0.8 (± 3.12)		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts from Baseline in Coagulation Parameters (Activated Partial Thromboplastin Time (aPTT))

End point title	Parts A and C: Number of Participants With Shifts from Baseline in Coagulation Parameters (Activated Partial Thromboplastin Time (aPTT))[27][28]

End point description:

Activated partial thromboplastin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of aPTT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of aPTT at baseline to high values postbaseline. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 269

Notes:

[27] - 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: Only descriptive statistics were planned for this endpoint.

[28] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Shift to Low (n=6,40)	0	5		
Shift to High (n=5,36)	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Change From Baseline in Growth Parameters (Weight for Age Percentile)

End point title	Parts A and C: Change From Baseline in Growth Parameters (Weight for Age Percentile)[29][30]

End point description:

WHO child growth standards (WHO Child Growth Standards, 2006) was used to calculate the weight for age percentile in the infantile-onset participants. The 2000 CDC Growth Charts was used to calculate the weight for age percentile for later-onset participants. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[29] - 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: Only descriptive statistics were planned for this endpoint.

[30] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	17		
Units: percentile				
arithmetic mean (standard deviation)	12.2 (± 12.84)	-2.7 (± 9.47)		

Statistical analyses

No statistical analyses for this end point

Primary: Part C: Change From Baseline in Growth Parameters (Weight for Length Ratio)

End point title	Part C: Change From Baseline in Growth Parameters (Weight for Length Ratio)[31][32]

End point description:

As pre-specified in the protocol, weight for length ratio was assessed only for the participants with infantile-onset SMA. ITT set included all participants who received at least one dose of nusinersen in the

current study. 'Subjects analysed' signifies number of participants evaluable for this outcome measure at the specified time point. '999' signifies that since only one participant was evaluated, SD was not estimable.

End point type	Primary

End point timeframe:

Baseline, Day 302

Notes:

[31] - 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: Only descriptive statistics were planned for this endpoint.

[32] - 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: Part C arm was planned to be analysed for this end point.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ratio				
arithmetic mean (standard deviation)	0.005 (± 999)			

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (Prothrombin Time (PT))

End point title	Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (Prothrombin Time (PT))[33][34]

End point description:

Prothrombin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of PT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of PT at baseline to high values postbaseline. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 269

Notes:

[33] - 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: Only descriptive statistics were planned for this endpoint.

[34] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Shift to Low (n=6,34)	0	0		
Shift to High (n=6,32)	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Part C: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio)

End point title	Part C: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio)[35][36]

End point description:

As pre-specified in the protocol, head to chest circumference ratio was assessed only for the participants with infantile-onset SMA. '99999' signifies that since one or no participant was evaluable, standard deviation (SD) was not estimated. ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Baseline, Day 302

Notes:

[35] - 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: Only descriptive statistics were planned for this endpoint.

[36] - 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: Part C arm was planned to be analysed for this end point.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ratio				
arithmetic mean (standard deviation)	0.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (International Normalized Ratio (INR))

End point title	Parts A and C: Number of Participants With Shifts From

	Baseline in Coagulation Parameters (International Normalized Ratio (INR))[37][38]

End point description:

INR was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of INR at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of INR at baseline to high values postbaseline. The category with at least one participant with shift from baseline in INR ratio is reported. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 269

Notes:

[37] - 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: Only descriptive statistics were planned for this endpoint.

[38] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
Shift to Low (n=6,40)	0	3		
Shift to High (n=6,39)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Change From Baseline in Urine Total Protein

End point title	Parts A and C: Change From Baseline in Urine Total

End point description:

Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[39] - 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: Only descriptive statistics were planned for this endpoint.

[40] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	29		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)	0.010 (± 0.1235)	-0.692 (± 3.7040)		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Number of Participants With Neurological Examination Abnormalities Reported as AEs

End point title	Parts A and C: Number of Participants With Neurological Examination Abnormalities Reported as AEs[41][42]

End point description:

Participants with abnormalities in neurological examinations recorded as AEs were reported.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[41] - 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: Only descriptive statistics were planned for this endpoint.

[42] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: participants				
number (not applicable)				
Vestibular Disorder	0	1		
Asthenia	0	1		
Gait Disturbance	0	1		
Balance Disorder	0	1		
Disturbance in Attention	0	1		
Paraesthesia	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Percentage of Participants With a Postbaseline Corrected QT Interval Using Fridericia's Formula (QTcF) of > 500 milliseconds (msec) and an Increase From Baseline to any Postbaseline Timepoint in QTcF of > 60 msec

End point title	Parts A and C: Percentage of Participants With a Postbaseline Corrected QT Interval Using Fridericia's Formula (QTcF) of > 500 milliseconds (msec) and an Increase From Baseline to any Postbaseline Timepoint in QTcF of > 60 msec[43][44]

End point description:

As a part of safety assessment, QTcF was evaluated for determining the incidence of clinically relevant abnormalities. Post baseline QTcF of > 500 msec and maximum increase from baseline to post baseline QTcF > 60 msec was considered as a criteria for clinically relevant abnormality in ECG. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[43] - 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: Only descriptive statistics were planned for this endpoint.

[44] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	39		
Units: percentage of participants				
number (not applicable)				
Maximum Increase from Baseline QTcF>60msec	0	0		
Maximum Post Baseline QTcF > 500 msec	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and C: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements

End point title	Parts A and C: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements[45][46]

End point description:

Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study.

End point type	Primary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[45] - 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: Only descriptive statistics were planned for this endpoint.

[46] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	40		
Units: percentage of participants				
number (not applicable)	0	2.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Percentage of Hammersmith Infant Neurological Examination (HINE) Section 2 Motor Milestone Responders for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

End point title	Part B Infantile-onset SMA: Percentage of Hammersmith Infant Neurological Examination (HINE) Section 2 Motor Milestone Responders for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group[47]

End point description:

Section 2 of HINE was used to assess motor milestones of participants. It's composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, & walking. Motor milestone responder: a participant that demonstrated atleast a 2-point increase in ability to kick category or increase to maximal score on that category or a 1-point increase in motor milestones category of head control, rolling, sitting, crawling, standing, or walking & demonstrated improvement in more categories than worsening. Participants who died or withdrew from study were considered as non-responders. A matched sham set was defined per protocol for analysis of this outcome measure. Matched sham set comprised of sham control participants of CS3B study (2013-004422-29) identified by a matching algorithm& all of 50/28 mg participants in the ITT set.

End point type	Secondary

End point timeframe:

Baseline up to Day 183

Notes:

[47] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	CS3B Matched Sham Control Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	41	9		
Units: percentage of responders				
number (not applicable)				

Ability to kick: At least a 2-point increase	18	0		
Ability to kick: Achievement of touching toes	8	0		
Head control: at least a 1-point increase	46	0		
Rolling: at least a 1-point increase	28	0		
Sitting: at least a 1-point increase	30	0		
Crawling: at least a 1-point increase	6	0		
Standing: at least a 1-point increase	14	0		
Walking: at least a 1-point increase	0	0		
Improvement in more categories than worsening	58	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen[48]

End point description:

The CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. It included 16 items (capturing neck, trunk, and proximal and distal limb strength), nine of which were scored 0, 1, 2, 3, or 4, five were scored as 0, 2, or 4, one was scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4 with greater scores indicating greater muscle strength. Total scores ranged from 0 (worst possible score) and 64 (best possible score). The change from baseline to Day 302 in the CHOP-INTEND total score was analyzed using the joint-rank methodology to account for mortality. ITT set included all participants who were randomized and received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[48] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: score on scale				
least squares mean (confidence interval 95%)	37.3 (29.1 to 45.5)	38.3 (32.7 to 44.0)		

Statistical analyses

Statistical analysis title	Change From Baseline in CHOP INTEND Total Score
Comparison groups	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8484 [49]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.29
upper limit	11.299
Variability estimate	Standard error of the mean
Dispersion value	5.251

Notes:

[49] - ANCOVA model used rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

Secondary: Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of Neurofilament Light Chain (NF-L) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

End point title	Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of Neurofilament Light Chain (NF-L) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group[50]

End point description:

The change from baseline in the plasma concentration of NF-L was compared to the study CS3B (2013-004422-29) matched sham control group. Joint rank methodology was used for the analysis to account for mortality. The change from baseline data was reported in terms of least square geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. As stated in protocol a matched sham set was defined for the analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set.

End point type	Secondary

End point timeframe:

Baseline, Day 183

Notes:

[50] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	CS3B Matched Sham Control Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	20		
Units: ratio				
least squares mean (confidence interval 95%)	0.06 (0.05 to 0.06)	0.70 (0.43 to 1.12)		

Statistical analyses

Statistical analysis title	Change From Baseline in NF-L Plasma Concentration
Comparison groups	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen v CS3B Matched Sham Control Group
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [51]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.14

Notes:

[51] - ANCOVA model was used with treatment as a fixed effect and adjustment for each participant disease duration at screening, baseline log plasma NF-L and baseline CHOP INTEND total score.

Secondary: Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

End point title	Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group[52]

End point description:

Section 2 of the HINE was used to assess motor milestones of the participants. It's composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each category, 3 to 5 levels can be achieved. The total HINE section 2 motor milestones score was calculated as sum of each level & ranged from 0 to 26, higher score indicating improvement in motor milestones. A negative change from baseline indicates decline in motor milestones.Change from baseline in HINE section 2 motor milestones total score was compared to study CS3B (2013-004422-29) matched sham control group, was analysed using joint rank methodology. As stated in protocol a matched sham set was defined for analysis of this outcome measure. Matched sham set comprised of sham control participants of CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in ITT set.

End point type	Secondary

End point timeframe:

Baseline, Day 183

Notes:

[52] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	CS3B Matched Sham Control Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	20		
Units: score on scale				
least squares mean (confidence interval 95%)	43.1 (39.0 to 47.2)	16.5 (9.9 to 23.0)		

Statistical analyses

Statistical analysis title	Change From Baseline in HINE Section Total Score
Comparison groups	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen v CS3B Matched Sham Control Group
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [53]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	26.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.812
upper limit	34.526
Variability estimate	Standard error of the mean
Dispersion value	4.009

Notes:

[53] - ANCOVA model was used, rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

Secondary: Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen[54]

End point description:

Section 2 of the HINE was used to assess motor milestones of the participants. It’s composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each of these categories, participants can progress from complete absence of a motor ability (the lowest level in each category) through multiple milestones (2 to 4 levels in each category) to the highest level within the category. The total motor milestones score for HINE section was calculated as the sum of each level and ranged from 0 to a maximum score of 26, higher score indicating improvement in motor milestones. ITT set included all participants who were randomized and received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[54] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: score on scale				
least squares mean (confidence interval 95%)	33.9 (26.9 to 41.0)	40.0 (35.1 to 44.9)		

Statistical analyses

Statistical analysis title	Change From Baseline in HINE Section Total Score
Comparison groups	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1734 [55]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	6.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.693
upper limit	14.939
Variability estimate	Standard error of the mean
Dispersion value	4.497

Notes:

[55] - ANCOVA model used rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

Secondary: Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

End point title	Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group[56]

End point description:

Permanent ventilation was defined as tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days in absence of an acute reversible event. An independent endpoint adjudication committee (EAC) determined date at which a participant was considered to have met protocol-specified criteria of an acute reversible event. Only events that were adjudicated by the EAC as meeting the criteria for permanent ventilation or death were included in analysis. As stated in protocol a matched sham set was defined for analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set. '99999' signifies that median and upper range of 95% confidence interval (CI) were not estimable due to low number events of permanent ventilation or death.

End point type	Secondary

End point timeframe:

Screening up to Day 399

Notes:

[56] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	CS3B Matched Sham Control Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	20		
Units: weeks				
median (confidence interval 95%)	99999 (39.86 to 99999)	19.1 (10.00 to 31.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen[57]

End point description:

The change from baseline in plasma concentration of NF-L was analysed using the joint rank methodology to account for mortality. The change from baseline data was reported in terms of LS geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who were randomized and received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 64

Notes:

[57] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: ratio				
least squares mean (confidence interval 95%)	0.23 (0.16 to 0.32)	0.12 (0.09 to 0.15)		

Statistical analyses

Statistical analysis title	Change From Baseline in NF-L Plasma Concentration
Comparison groups	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [58]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.78

Notes:

[58] - ANCOVA model was used with treatment as a fixed effect and adjustment for each participant disease duration at screening, baseline log plasma NF-L and baseline CHOP INTEND total score.

Secondary: Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus 12/12mg Nusinersen[59]

End point description:

Permanent ventilation was defined as tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days in the absence of an acute reversible event. An independent EAC determined the date at which a participant was considered to have met the protocol-specified criteria of an acute reversible event. Only events that were adjudicated by the EAC as meeting the protocol defined criteria for permanent ventilation or death was included in the analysis. ITT set included all participants who were randomized and received at least one dose of nusinersen. ' 99999' signifies that median or upper range of 95% confidence interval (CI) were not estimable due to low number events of permanent ventilation or death.

End point type	Secondary

End point timeframe:

Screening up to Day 399

Notes:

[59] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: weeks				
median (confidence interval 95%)	24.7 (14.43 to 99999)	99999 (39.86 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

End point title	Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group[60]

End point description:

Time to death was determined by an independent EAC. Time to death (overall survival) was compared to the study CS3B (2013-004422-29) matched sham control group. As stated in protocol a matched sham set was defined for the analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set. '99999' signifies that median and 95% CI were not estimable due to low number of events of death.

End point type	Secondary

End point timeframe:

Screening up to Day 399

Notes:

[60] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	CS3B Matched Sham Control Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	20		
Units: weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	33.6 (11.29 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From Baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Change From Baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen [61]

End point description:

HFMSE scale was a tool used to assess motor function in children with later-onset SMA. The original 20 item Hammersmith Functional Motor Scale was expanded to include 13 additional adapted items from the Gross Motor Function Measure to improve sensitivity for the higher functioning ambulant population. Each item is scored 0 (unable), 1 (performs with modification or adaptation) or 2 (able) and the total score was calculated by summing the 33 items and ranged from 0 to 66 with higher scores indicating greater motor function. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[61] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	15		
Units: score on scale				
least squares mean (confidence interval 95%)	2.6 (0.2 to 5.1)	3.3 (1.5 to 5.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From Baseline in Revised Upper Limb Module (RULM) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Change From Baseline in Revised Upper Limb Module (RULM) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen[62]

End point description:

RULM test was developed to assess upper limb functional abilities. RULM test: total 20 items. First item assessed on 7-point scale (0:No useful function to 6-Can abduct both arms simultaneously, elbows in extension in full circle until they touch above head). This item did not contribute to total score. For remaining 19 items, 18 items assessed on 3-point scale: 0-Unable to achieve independently; 1-Modified method but achieves goal independent of physical assistance from another person; 2-Normal -achieves goal without any assistance. One remaining item, assessed as 0 or 1. For each item, score was collected on left & right side. Derived total score=summing scores of 19 individual items ranging from 0-if participant fails all activities to 37-if participant achieves all activities. Higher scores=increased upper limb function. ITT set included all participants who were randomized and received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[62] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	16		
Units: score on scale				
least squares mean (confidence interval 95%)	1.8 (-0.8 to 4.4)	2.5 (0.7 to 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus 12/12mg Nusinersen [63]

End point description:

Time to death was determined by an independent EAC. ITT set included all participants who were randomized and received at least one dose of nusinersen. '99999' signifies that median and 95% CI was not estimable due to low number events of death.

End point type	Secondary

End point timeframe:

Screening up to Day 399

Notes:

[63] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: weeks				
median (confidence interval 95%)	99999 (24.71 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Number of New World Health Organization (WHO) Motor Milestones for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Number of New World Health Organization (WHO) Motor Milestones for 50/28mg Nusinersen Versus 12/12mg Nusinersen[64]

End point description:

The WHO motor milestones were a set of six milestones in motor development: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone and walking alone. The examiner recorded an overall rating of the participant's emotional state and then for each milestone one of the following four classifications: no (inability) - child tried but failed to perform the milestone, no (refusal) - child refused to perform despite being calm and alert, yes - child was able to perform the milestone, unable to test - could not be tested because of irritability, drowsiness or sickness. Mean of number of new milestones achieved was calculated and reported in this outcome measure. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[64] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	16		
Units: motor milestones				
arithmetic mean (standard deviation)	0.0 (± 0.00)	0.3 (± 1.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Change From Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) for 50/28mg Nusinersen Versus 12/12mg Nusinersen[65]

End point description:

ACEND instrument was designed to quantify caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA. The ACEND included a total of seven domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance, and each domain comprised several items. The total score for each domain was calculated on a scale of 0 to 100, with a higher score indicating a decreased caregiver burden. A negative change from baseline indicates an increased caregiver burden. ITT set included all participants who were randomized and received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[65] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	16		
Units: score on scale				
least squares mean (confidence interval 95%)				
Feeding/Grooming/Dressing Total Score	7.9 (-4.8 to 20.6)	8.3 (-0.2 to 16.7)		
Sitting/Play Total Score	10.3 (0.6 to 20.0)	10.1 (3.6 to 16.6)		
Transfers Total Score	-0.0 (-10.9 to 10.9)	9.9 (2.6 to 17.2)		
Mobility Total Score	6.9 (-7.2 to 20.9)	8.1 (-0.9 to 17.0)		
Time Total Score	-4.4 (-17.9 to 9.2)	11.9 (2.9 to 20.9)		
Emotion Total Score	2.6 (-8.7 to 13.9)	2.5 (-5.0 to 10.0)		
Finance Total Score	-7.7 (-20.9 to 5.6)	7.8 (-0.7 to 31.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From (Ratio to) Baseline in CSF Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Change From (Ratio to) Baseline in CSF Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen[66]

End point description:

The change from baseline data was reported in terms of geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 279

Notes:

[66] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	16		
Units: pg/mL				
geometric mean (confidence interval 95%)	0.34 (0.23 to 0.50)	0.34 (0.25 to 0.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen[67]

End point description:

The change from baseline data was reported in terms of geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[67] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	16		
Units: pg/mL				
geometric mean (confidence interval 95%)	0.28 (0.14 to 0.56)	0.35 (0.24 to 0.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From Baseline in Pediatric Quality of Life Inventory™ (PedsQL) for 50/28mg Nusinersen Versus 12/12mg Nusinersen

End point title	Part B Later-onset SMA: Change From Baseline in Pediatric Quality of Life Inventory™ (PedsQL) for 50/28mg Nusinersen

	Versus 12/12mg Nusinersen[68]

End point description:

PedsQL was used to measure health related quality of life (HRQOL) in children & adolescents. PedsQL generic core scale included assessment of physical functioning, emotional functioning, social functioning, and school functioning [PedsQL Inventory total score (PQLI)] and PedsQL Neuromuscular Module [Neuromuscular total score (PQLN)] measured HRQOL dimensions specific to with neuromuscular disorders, including SMA. Four dimensions were collected,each item scored on a 5-point ordinal scale (0=Never to 4=Almost Always). Items were reversed scored and were linearly transformed to a 0-100 scale. Total scale score was calculated as sum of all items over number of items answered on all scales. If more than 50% of items or more were missing, scale score was not computed. Higher scores indicated better health related quality of life. ITT set. Subjects analysed: number of participants evaluable for this endpoint. 'Number analysed (n)':number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[68] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	16		
Units: score on scale				
least squares mean (standard error)				
PQLI-Total Score-Subject (n=4,12)	-5.1 (± 4.73)	3.8 (± 2.61)		
PQLI-Total Score-Parent (n=7,14)	-9.6 (± 4.32)	-6.9 (± 2.96)		
PQLN-Total Score-Subject (n=4,12)	-4.8 (± 3.41)	10.4 (± 1.91)		
PQLN-Total Score-Parent (n=7,16)	-6.4 (± 4.25)	-0.7 (± 2.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Hematology Parameters)

End point title	Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Hematology Parameters)[69]

End point description:

Hematology parameters included complete blood cell count, with dierential and platelet count, and absolute neutrophil count. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified hematology parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[69] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Basophils Shift to Low (n=22,46,8,16)	0	2	0	0
Basophils Shift to High (n=12,24,5,13)	7	17	4	8
Basophils/Leukocytes Shift to High (n=11,21,4,9)	7	14	3	9
Eosinophils Shift to Low (n=20,47,7,16)	0	7	1	0
Eosinophils Shift to High (n=19,43,5,14)	6	15	0	1
Eosinophil/Leukocyte Shift toLow(n=21,47,8,16)	0	4	0	0
Eosinophil/Leukocyte Shift to High(n=15,28,5,12)	8	12	1	5
Hematocrit Shift to Low (n=20,43,8,16)	6	12	0	2
Hematocrit Shift to High (n=22,47,8,15)	4	10	2	1
Hemoglobin Shift to Low (n=22,45,7,14)	11	18	0	2
Hemoglobin Shift to High (n=23,46,8,16)	3	2	0	0
Lymphocytes Shift to Low (n=22,47,8,16)	3	6	1	1
Lymphocytes Shift to High (n=19,41,7,14)	4	14	2	2
Lymphocyte Atypical Shift to High(n=1,7,8,16)	0	5	0	0
LymphocyteAtypical/LeukocyteShifttoHighn=1,7,8,16	0	4	0	0
Lymphocyte/Leukocyte Shift to Low(n=22,45,8,16)	4	5	1	2
Lymphocyte/Leukocyte Shift to High(n=20,43,7,16)	4	7	3	1
Ery Mean Corpuscular Vol Shift to Lown=5,10,8,16	2	2	0	0
Ery Mean Corpuscular Vol Shift to Highn=4,8,8,16	1	2	0	0
Monocytes Shift to Low (n=22,46,7,15)	5	12	1	6
Monocytes Shift to High (n=20,42,8,16)	5	13	2	2
Monocytes/Leukocytes Shift to Low (n=21,44,6,14)	7	20	1	9
Monocytes/Leukocytes Shift to High n=20,45,8,16	3	9	1	1
Neutrophils Shift to Low (n=19,42,5,16)	5	9	1	2
Neutrophils Shift to High (n=21,46,8,16)	11	13	1	1
Neutrophils/Leukocytes Shift to Low n=19,39,7,16	4	13	4	0
Neutrophils/Leukocytes ShifttoHigh n=21,45,7,16	6	6	1	1
Platelets Shift to Low (n=23,47, 8,16)	1	2	0	1

Platelets Shift to High (n=10,28,6,15)	4	14	1	4
Erythrocytes Shift to Low (n=23,46,6,15	4	10	0	0
Erythrocytes Shift to High (n=22,47,8,13)	3	6	1	0
Leukocytes Shift to Low (n=21,44,8,16)	4	13	2	0
Leukocytes Shift to High (n=21,41,7,15)	10	15	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants with TEAEs and TESAEs

End point title	Part B: Number of Participants with TEAEs and TESAEs[70]

End point description:

AE was any unfavorable and unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An SAE was any untoward medical occurrence that at any dose resulted in death, in the view of the Investigator, placed the participant at immediate risk of death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a birth defect. AE was regarded as treatment-emergent if it was present prior to receiving the first dose of nusinersen in the current study and subsequently worsened in severity or was not present prior to receiving the first dose of nusinersen and subsequently appeared. Safety set included all participants who received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

From the first dose of the study drug up to Day 399

Notes:

[70] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
TEAEs	22	45	7	14
TESAEs	18	30	4	2

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)

End point title	Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)

[71]

End point description:

Blood chemistry parameters included protein, albumin, creatinine, blood urea nitrogen, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, and creatine kinase. Parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. Categories with at least one participant with shift from baseline in these parameters are reported. Safety set included all participants who received at least a dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[71] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Albumin Shift to Low (n=20,46,8,15)	6	13	1	1
Albumin Shift to High (n=23,50,8,16)	1	2	0	0
Alkaline Phosphatase Shift to Low (n=23,50,8,16)	0	3	0	0
Alkaline Phosphatase Shift to High (n=23,50,8,16)	3	3	0	0
Alanine AminotransferaseShift to Low n=23,50,8,16	0	0	0	1
Alanine AminotransferaseShift to Highn=14,39,6,15	4	14	0	3
AspartateAminotransferaseShifttoHigh n=21,45,7,16	5	9	0	1
Bicarbonate Shift to Low (n=5,14,3,4)	4	12	3	4
Bicarbonate Shift to High (n=22,49,8,16)	1	1	0	0
Direct Bilirubin Shift to Low (n=22,45,8,16)	1	0	0	0
Bilirubin Shift to Low (n=21,49,8,16)	2	2	0	1
Bilirubin Shift to High (n=20,45,8,16)	1	1	0	0
Indirect Bilirubin Shift to Low (n=22,46,2,4)	11	21	2	3
Calcium Shift to Low (n=23,50,8,15)	1	4	2	1
Calcium Shift to High (n=19,45,8,15)	8	17	0	0
Creatine Kinase Shift to High (n=14,27,6,10)	6	12	3	3
Chloride Shift to Low (n=23,50,8,16)	3	3	0	1
Chloride Shift to High (n=23,48,7,16)	3	6	1	1
Creatinine Shift to Low (n=2,5,0,1)	2	5	0	1
Creatinine Shift to High (n=23,50,8,16)	0	1	0	0
Cystatin C Shift to Low(n=23,48,8,16)	2	0	1	1

Cystatin C Shift to High(n=23,48,8,16)	2	1	0	0
Gamma GlutamylTransferase ShifttoLown=18,45,8,16	7	11	0	1
GammaGlutamylTransferase ShifttoHighn=23,49,8,16	2	5	0	3
Glucose Shift to Low(n=23,49,8,16)	0	2	0	1
Glucose Shift to High(n=20,44,7,15)	6	17	2	6
Potassium Shift to Low(n=23,50,8,16)	1	2	0	1
Potassium Shift to High(n=21,44,8,16)	5	15	3	4
Lactate Dehydrogenase Shift to High(n=0,1,8,16)	0	1	0	0
Magnesium Shift to High(n=3,5,8,16)	0	2	0	0
Phosphate Shift to Low(n=23,50,8,16)	3	2	0	0
Phosphate Shift to High(n=18,42,4,13)	5	16	2	10
Protein Shift to Low(n=21,48,7,15)	7	9	1	2
Protein Shift to High(n=23,47,8,16)	2	6	0	2
Sodium Shift to Low(n=20,47,7,15)	3	15	2	3
Sodium Shift to High(n=23,50,8,16)	0	0	0	1
Urea Nitrogen Shift to Low(n=23,44,8,16)	1	3	2	1
Urea Nitrogen Shift to High(n=23,50,8,15)	0	0	2	1

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants with Shifts from Baseline in Urinalysis

End point title	Part B: Number of Participants with Shifts from Baseline in Urinalysis[72]

End point description:

Urinalysis included assessments of urine total protein, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, RBC , WBC, epithelial cells, bacteria, casts and crystals. These parameters were flagged as low, normal, or high relative to parameter’s normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high, positive, abnormal or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, negative, absent, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Safety set included all participants who received at least one dose of nusinersen. ‘Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[72] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Specific Gravity Shift to Low (n=20,47,8,16)	2	2	1	1
Specific Gravity Shift to High (n=22,50,7,15)	3	3	1	1
pH Shift to Low (n=21,48,8,16)	2	1	0	1
pH Shift to High (n=21,47,8,16)	5	8	1	1
Protein High/positive (n=18,45,5,13)	12	27	3	9
Glucose High/positive (n=21,46,8,16)	2	2	0	0
Ketones High/positive (n=20,44,8,14)	5	16	4	4
Occult Blood High/positive (n=16,43,7,14)	4	12	2	1
RBC High/positive (n=13,26,7,12)	0	3	0	0
WBC High/positive (n=15,25,6,10)	3	12	3	4
Epithelial Cells High/positive (n=2,7,5,3)	0	6	5	2
Bacteria High/positive (n=10,18,2,8)	10	18	2	8
Casts High/positive (n=3,3,8,16)	0	1	0	0
Crystals High/positive (n=5,4,8,16)	2	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Shifts From Baseline in CSF Parameters

End point title	Part B: Number of Participants With Shifts From Baseline in CSF Parameters[73]

End point description:

CSF parameters included cell count, total protein, and glucose. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Safety set included all participants who received at least one dose of nusinersen. Subjects analyzed indicates number of participants evaluable for this outcome measure. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[73] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	47	8	16
Units: participants				
Glucose Shift to Low (n=16,36,7,12)	4	3	1	0
Glucose Shift to High (n=19,46,8,16)	0	1	0	0
Protein Shift to Low (n=18,45,5,11)	2	6	0	4
Protein Shift to High (n=12,25,8,15)	4	7	2	2
Erythrocytes Shift to Low (n=18,47,8,15)	1	0	0	0
Erythrocytes Shift to High (n=14,37,5,11)	3	9	2	7
Leukocytes Shift to Low (n=17,47,8,11)	1	2	0	1
Leukocytes Shift to High (n=16,38,8,11)	1	5	0	4

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Shift From Baseline in ECGs

End point title	Part B: Number of Participants With Shift From Baseline in ECGs[74]

End point description:

The ECGs were assessed by the investigator to be normal, abnormal and abnormal AE. The number of participants with ECG shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) was assessed. Shift from baseline to worst post-baseline values were reported. The categories with at least one participant with shift from baseline in ECG are reported. Safety set included all participants who received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[74] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Normal to Normal	2	7	0	0
Normal to Abnormal, not AE	9	10	2	4
Normal to Abnormal, AE	1	0	0	0
Abnormal, not AE to Abnormal, not AE	12	30	6	12
Abnormal, not AE to Abnormal, AE	1	2	0	0
Unknown to Abnormal, not AE	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Abnormalities in Vital Sign Parameters

End point title	Part B: Number of Participants With Abnormalities in Vital Sign Parameters [75]

End point description:

Vital sign assessment included temperature, pulse rate systolic blood pressure, diastolic blood pressure, and respiratory rate. As pre-specified in protocol, the criteria for determining potentially clinically relevant abnormalities in vital signs included: temperature < 36 and > 38 degrees C, pulse rate < 60 and > 100 bpm, systolic blood pressure < 90, > 140 and > 160 mmHg, diastolic blood pressure < 50, > 90 and > 100 mmHg and respiratory rate < 12 and > 20 breaths per minute. The categories with at least one participant with clinically relevant vital sign abnormalities are reported. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[75] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Temperature <36.0 C (n=25,50,8,16)	6	23	3	7
Temperature >38.0 C (n=25,50,8,16)	0	6	0	1
Pulse Rate <60 bpm (n=25,50,8,16)	1	2	0	0
Pulse Rate >100 bpm (n=25,50,8,16)	25	50	8	16
Systolic Blood Pressure <90 mmHg (n=25,49,8,16)	24	47	7	10
Systolic Blood Pressure >140 mmHg (n=25,49,8,16)	3	0	0	0
Diastolic Blood Pressure <50 mmHg (n=25,49,8,16)	22	44	4	10
Diastolic Blood Pressure >90 mmHg(n=25,49,8,16)	5	8	1	2
Diastolic Blood Pressure >100 mmHg(n=25,49,8,16)	2	0	0	1
Respiratory Rate >20 breaths/min (n=25,50,8,16)	25	50	8	16

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in Growth Parameters (Body Height)

End point title	Part B: Change From Baseline in Growth Parameters (Body Height)[76]

End point description:

Body height was measured for all participants (infantile-onset and later-onset SMA). Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[76] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	4	1	8
Units: cm				
arithmetic mean (standard deviation)	8.00 (± 99999)	10.25 (± 2.217)	11.2 (± 99999)	6.9 (± 3.65)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Head Circumference)

End point title	Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Head Circumference)[77]

End point description:

Head circumference was measured in participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[77] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	35		
Units: cm				
arithmetic mean (standard deviation)	4.52 (± 1.703)	5.50 (± 2.766)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Chest Circumference)

End point title	Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Chest Circumference)[78]

End point description:

Chest circumference was measured in participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[78] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	35		
Units: cm				
arithmetic mean (standard deviation)	5.67 (± 4.868)	6.64 (± 6.362)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Arm Circumference)

End point title	Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Arm Circumference)[79]

End point description:

Arm circumference was measured in participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[79] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	35		
Units: cm				
arithmetic mean (standard deviation)	0.45 (± 2.141)	1.16 (± 2.144)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in Growth Parameters (Weight for Length Percentile)

End point title	Part B: Change From Baseline in Growth Parameters (Weight for Length Percentile)[80]

End point description:

As pre-specified in the protocol, weight for length percentile was assessed only for the participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[80] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	30	0[81]	0[82]
Units: percentile				
arithmetic mean (standard deviation)	-4.23 (± 35.817)	6.05 (± 40.119)	()	()

Notes:

[81] - As the number of subjects analyzed was zero, mean and SD was not calculated.

[82] - As the number of subjects analyzed was zero, mean and SD was not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in Growth Parameters (Weight for Age Percentile)

End point title	Part B: Change From Baseline in Growth Parameters (Weight for Age Percentile)[83]

End point description:

WHO child growth standards (WHO Child Growth Standards, 2006) was used to calculate the weight for age percentile in the infantile-onset participants. The 2000 CDC Growth Charts was used to calculate the weight for age percentile for later-onset participants. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[83] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	35	7	16
Units: percentile				
arithmetic mean (standard deviation)	-6.70 (± 23.133)	-3.60 (± 35.202)	9.1 (± 20.23)	-0.3 (± 6.96)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Later-onset SMA: Change From Baseline in Growth Parameters (Ulnar Length)

End point title	Part B Later-onset SMA: Change From Baseline in Growth Parameters (Ulnar Length)[84]

End point description:

Ulnar length was measured in participants with later-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[84] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	16		
Units: cm				
arithmetic mean (standard deviation)	2.8 (± 4.16)	1.2 (± 1.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio)

End point title	Part B: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio)[85]

End point description:

As pre-specified in the protocol, head to chest circumference ratio was assessed only for the participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint. '99999' signifies that since one or no participant was evaluable, SD was not estimated.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[85] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	35		
Units: ratio				
arithmetic mean (standard deviation)	-0.03 (± 0.085)	-0.05 (± 0.269)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (PT)

End point title	Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (PT)[86]

End point description:

Prothrombin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of PT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of PT at baseline to high values postbaseline. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 279

Notes:

[86] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Shift to Low (n=22,48,8,15)	3	6	1	1
Shift to High (n=20,45,8,14)	2	6	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (aPTT)

End point title	Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (aPTT)[87]

End point description:

aPTT was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of aPTT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of aPTT at baseline to high values postbaseline. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 279

Notes:

[87] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed

for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Shift to Low (n=22,48,7,16)	4	14	2	2
Shift to High (n=17,40,8,15)	6	7	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (INR)

End point title	Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (INR)[88]

End point description:

INR was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of INR at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of INR at baseline to high values postbaseline. The category with at least one participant with shift from baseline in INR ratio is reported. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of specified parameter.

End point type	Secondary

End point timeframe:

Baseline up to Day 279

Notes:

[88] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
Shift to Low (n=22,49,8,16)	1	5	0	0
Shift to High (n=21,44,8,16)	2	6	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in Urine Total Protein

End point title	Part B: Change From Baseline in Urine Total Protein[89]

End point description:

Safety set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[89] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	18	3	11
Units: g/L				
arithmetic mean (standard deviation)	-0.130 (± 0.4126)	-3.274 (± 14.1387)	-0.213 (± 0.2873)	0.004 (± 0.0608)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants With Neurological Examination Abnormalities Reported as AEs

End point title	Part B: Number of Participants With Neurological Examination Abnormalities Reported as AEs[90]

End point description:

Participants with abnormalities in neurological examinations recorded as AEs were reported.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[90] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: participants				
number (not applicable)				
Muscular Weakness	0	1	0	0
Bulbar Palsy	1	0	0	0
Tremor	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements

End point title	Part B: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements[91]

End point description:

Safety set included all participants who received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[91] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	50	8	16
Units: percentage of participants				
number (not applicable)	4	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A, B and C: Percentage of Time of Hospitalization

End point title	Parts A, B and C: Percentage of Time of Hospitalization

End point description:

Parts A, B and C: ITT set included all participants who received at least one dose of nusinersen in the

current study.

End point type	Secondary

End point timeframe:

Parts A, B, and C: Baseline up to Day 302

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	25	50	8
Units: percentage of days				
median (full range (min-max))	0 (0 to 2)	6.4 (0 to 100)	1.9 (0 to 100)	0.0 (0 to 8)

End point values	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	40		
Units: percentage of days				
median (full range (min-max))	0.0 (0 to 11)	1.34 (0.3 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Percentage of Participants With a Postbaseline QTcF of > 500 msec and an Increase from Baseline to any Postbaseline Timepoint in QTcF of > 60 msec

End point title	Part B: Percentage of Participants With a Postbaseline QTcF of > 500 msec and an Increase from Baseline to any Postbaseline Timepoint in QTcF of > 60 msec[92]

End point description:

As a part of safety assessment, QTcF was evaluated for determining the incidence of clinically relevant abnormalities. Post baseline QTcF of > 500 msec and maximum increase from baseline to post baseline QTcF > 60 msec was considered as a criteria for clinically relevant abnormality in ECG. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[92] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed

for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	49	8	15
Units: percentage of participants				
number (not applicable)	8	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A, B and C: Number of Participants With Hospitalizations

End point title	Parts A, B and C: Number of Participants With Hospitalizations

End point description:

Parts A, B and C: ITT set included all participants who received at least one dose of nusinersen in the current study.

End point type	Secondary

End point timeframe:

Parts A, B, and C: Baseline up to Day 302

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	25	50	8
Units: number of participants	1	19	26	3

End point values	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	40		
Units: number of participants	6	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A, B and C: Number of Participants With Clinical Global Impression of Change (CGIC)

End point title	Parts A, B and C: Number of Participants With Clinical Global Impression of Change (CGIC)

End point description:

The CGIC scale was a 7 point scale that required the clinician to assess how much the participant's illness had changed relative to a baseline state at the beginning of the intervention, where 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse. Higher rating indicates worsening of the condition. A separate CGIC assessment was performed by the Investigator (I) and caregiver (C). The categories with at least one participant having a CGIC score was reported. ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable for this endpoint. Number analysed 'n' indicates the number of participants evaluable for the specified category.

End point type	Secondary

End point timeframe:

Parts A, B, and C: Day 302

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	13	35	7
Units: participants				
CGIC-I-Very Much Improved	0	0	8	0
CGIC-I-Much Improved	1	10	20	3
CGIC-I-Minimally Improved	5	3	7	4
CGIC-I-No Change	0	0	0	0
CGIC-I-Minimally Worse	0	0	0	0
CGIC-C-Very Much Improved (n=6,13,35,7,16,24)	1	3	18	1
CGIC-C-Much Improved (n=6,13,35,7,16,24)	2	7	13	2
CGIC-C-Minimally Improved (n=6,13,35,7,16,24)	2	3	3	4
CGIC-C-No Change (n=6,13,35,7,16,24)	0	0	1	0
CGIC-C-Minimally Worse (n=6,13,35,7,16,24)	1	0	0	0

End point values	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	40		
Units: participants				
CGIC-I-Very Much Improved	1	0		
CGIC-I-Much Improved	5	5		

CGIC-I-Minimally Improved	9	19		
CGIC-I-No Change	1	14		
CGIC-I-Minimally Worse	0	2		
CGIC-C-Very Much Improved (n=6,13,35,7,16,24)	0	2		
CGIC-C-Much Improved (n=6,13,35,7,16,24)	8	6		
CGIC-C-Minimally Improved (n=6,13,35,7,16,24)	7	9		
CGIC-C-No Change (n=6,13,35,7,16,24)	1	5		
CGIC-C-Minimally Worse (n=6,13,35,7,16,24)	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A, B and C: Number of Serious Respiratory Events

End point title	Parts A, B and C: Number of Serious Respiratory Events
End point description:	
ITT set included all participants who received at least one dose of nusinersen in the current study.	
End point type	Secondary
End point timeframe:	
Parts A, B, and C: Baseline up to Day 399	

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	25	50	8
Units: number of events				
number (not applicable)	0	34	60	6

End point values	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	40		
Units: number of events				
number (not applicable)	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in the Parent Assessment of Swallowing Ability (PASA) Scale

End point title	Part A: Change From Baseline in the Parent Assessment of Swallowing Ability (PASA) Scale[93]

End point description:

PASA was assessed using a questionnaire. Caregivers were asked a series of questions regarding mealtime behavior of participant. PASA questionnaire was developed to assess signs & symptoms of dysphagia. It included 33 items across 4 domains: general feeding, drinking liquids, eating solid foods, & assessment of swallowing concerns. Items in domains general feeding, drinking liquids, & eating solid foods assessed with 5 levels of response scored as 4-Never,3-Rarely,2-Sometimes,1-Often,&0-Always. Domain for assessing swallowing concerns has 4 levels of responses scored as: 3-Strongly Disagree, 2-Disagree, 1-Agree, 0-Strongly Agree. Higher score= improvement. Negative change from baseline=decrease in swallowing ability. From domains 'drinking liquids' and 'eating solid foods', 2 items (attempted to drink liquids and eat solid foods) were assessed as "Yes"/"No", reported in another outcome measure. ITT set. 'Number analysed' =number of subjects evaluable for specified parameter.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[93] - 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: Part A arm was planned to be analysed for this endpoint.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: score on scale				
arithmetic mean (standard deviation)				
Had Difficulty Feeding Themselves	0.2 (± 0.41)			
Had to Suction Excess Saliva/Drool	0.0 (± 0.00)			
Not Able Eat as Much as Would Like	0.2 (± 0.41)			
Not Able Eat Food Variety Would Like	-0.2 (± 0.41)			
Been Tube-Fed	0.0 (± 0.00)			
Refused Liquid Foods (n=4)	0.0 (± 0.00)			
Difficulty Drinking Thin Liquids (n=4)	0.0 (± 0.00)			
Difficulty Drinking Thick Liquids (n=4)	0.0 (± 0.00)			
Cough/Clear Throat Swallow Liquid Food (n=4)	0.0 (± 0.00)			
Gagged or Choked on Liquid Food (n=4)	0.0 (± 0.00)			
Retching/Vomiting Drinking Liquids (n=4)	0.0 (± 0.00)			
Taken > 30 Minutes Drink Liquids (n=4)	0.0 (± 0.00)			
Refused Solid Foods	0.2 (± 0.41)			
Difficulty Swallowing Soft Foods	0.0 (± 0.00)			
Difficulty Swallowing Solid Foods	-0.2 (± 0.41)			
Had Difficulty Swallowing Pills	0.2 (± 0.98)			
Cough/Clear Throat Eat/Swallow Solid Food	0.2 (± 0.41)			
Had Food Stuck in Throat/Chest	0.0 (± 0.00)			

Gagged/Choked on Their Solid Food	0.2 (± 0.41)			
Retching/Vomiting Eating Solids	0.2 (± 0.41)			
Required Food to Be Cut Up	0.7 (± 1.21)			
Experienced/Shown Pain When Eating	0.0 (± 0.00)			
Has Taken > 30 Minutes Eat Solids	0.3 (± 0.52)			
Concern Child's Swallowing Ability	0.8 (± 1.72)			
Concerned About Child's Weight	1.2 (± 1.60)			
Concern Variety Foods Child Eats	0.7 (± 1.51)			
Concern Child Not Able Eat as Much	1.3 (± 1.51)			
Concern Child Unable Eat Variety	1.3 (± 1.37)			
Concern Not Get Goodness From Diet	1.8 (± 1.17)			
Concerned Child Aspirating Food	1.0 (± 1.55)			
Concern Child Choking When Eating	1.2 (± 1.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A, B and C: Number of Participants With Ventilator Use

End point title	Parts A, B and C: Number of Participants With Ventilator Use
End point description:	
ITT set included all participants who received at least a dose of nusinersen.	
End point type	Secondary
End point timeframe:	
Parts A, B, and C: Screening up to Day 302	

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	25	50	8
Units: participants	0	9	22	4

End point values	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	40		
Units: participants	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B Infantile-onset SMA: Percentage of Time on Ventilation

End point title	Part B Infantile-onset SMA: Percentage of Time on

End point description:

ITT set included all participants who received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline up to Day 302

Notes:

[94] - 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: Only descriptive statistics were planned for this endpoint.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: percentage of hours				
median (full range (min-max))	5.6 (0 to 100)	7.5 (0 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in the PASA Scale

End point title	Part B: Change From Baseline in the PASA Scale[95]

End point description:

PASA was assessed using a questionnaire. Caregivers were asked a series of questions regarding mealtime behavior of participant. The PASA questionnaire was developed to assess the signs and symptoms of dysphagia. It included 33 items across 4 domains. Items in domains of general feeding, drinking liquids, & eating solid foods are assessed with 5 levels of response scored as 4-Never, 3-Rarely, 2-Sometimes, 1-Often, & 0-Always. Domain for assessing swallowing concerns has 4 levels of responses scored as: 3-Strongly Disagree, 2-Disagree, 1-Agree, 0-Strongly Agree. Higher score= improvement.Negative change from baseline=decrease in swallowing ability. As planned, for part B of the study, the PASA scale was assessed for domain general feeding only. ITT set included all participants who received at least one a dose of nusinersen. 'Subjects analysed'=number of participants evaluable for this endpoint. 'Number analysed (n)'=number of participants evaluable for specified parameter.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[95] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	32	7	14
Units: score on scale				
arithmetic mean (standard deviation)				
Had Difficulty Feeding Themselves (n=7,29)	-1.6 (± 1.81)	-0.6 (± 1.55)	-0.4 (± 0.53)	0.3 (± 0.73)
Had To Suction Excess Saliva or Drool(n=7,31)	-1.7 (± 1.38)	-0.2 (± 1.58)	0.1 (± 0.38)	0.1 (± 0.36)
Not Able To Eat As Much As Would Like(n=7,31)	-1.6 (± 1.72)	-0.2 (± 1.45)	0.3 (± 0.95)	0.0 (± 0.39)
Not Able To Eat Food Variety They Like(n=7,29)	-1.6 (± 1.72)	-1.0 (± 1.18)	0.1 (± 0.69)	-0.4 (± 0.93)
Been Tube-Fed (n=9, 32)	-1.8 (± 2.11)	-0.9 (± 1.76)	0.0 (± 0.00)	0.0 (± 0.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and C: Change From Baseline in HFMSE Total Score

End point title	Parts A and C: Change From Baseline in HFMSE Total Score[96]

End point description:

HFMSE scale was a tool used to assess motor function in children with SMA. The original 20 item Hammersmith Functional Motor Scale was expanded to include 13 additional adapted items from the Gross Motor Function Measure to improve sensitivity for the higher functioning ambulant population. Each item is scored 0 (unable), 1 (performs with modification or adaptation) or 2 (able) and the total score was calculated by summing the 33 items and ranged from 0 to 66 with higher scores indicating greater motor function. ITT set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

End point type	Secondary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[96] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	38		
Units: score on scale				
arithmetic mean (standard deviation)	-0.8 (± 3.76)	1.8 (± 3.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and C: Change From Baseline in RULM Total Score

End point title	Parts A and C: Change From Baseline in RULM Total Score[97]

End point description:

RULM test was developed to assess upper limb functional abilities. RULM test: total 20 items. First item assessed on 7-point scale (0:No useful function to 6-Can abduct both arms simultaneously, elbows in extension in full circle until they touch above head). This item did not contribute to total score. For remaining 19 items, 18 items assessed on 3-point scale: 0-Unable to achieve independently; 1-Modified method but achieves goal independent of physical assistance from another person; 2-Normal -achieves goal without any assistance. One remaining item, assessed as 0 or 1. For each item, score was collected on left & right side. Derived total score=summing scores of 19 individual items ranging from 0-if participant fails all activities to 37-if participant achieves all activities. Higher scores=increased upper limb function. ITT set. Subjects analysed' signifies number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[97] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	37		
Units: score on scale				
arithmetic mean (standard deviation)	1.5 (± 1.52)	1.2 (± 2.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Infantile SMA-onset: Change From (Ratio to) Baseline in CSF Concentration of NF-L

End point title	Part B: Infantile SMA-onset: Change From (Ratio to) Baseline in CSF Concentration of NF-L[98]

End point description:

The change from baseline data was reported in terms of geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 279

Notes:

[98] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

End point values	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	50		
Units: pg/mL				
geometric mean (confidence interval 95%)	0.06 (0.05 to 0.08)	0.05 (0.04 to 0.06)		

Statistical analyses

Statistical analysis title	Change From Baseline in NF-L CSF Concentration
Comparison groups	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3785 [99]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.2

Notes:

[99] - ANCOVA model was used with treatment as a fixed effect and adjustment for each participant disease duration at screening, baseline log CSF NF-L and baseline CHOP INTEND total score.

Secondary: Parts A and C: Change From Baseline in ACEND Total Score

End point title	Parts A and C: Change From Baseline in ACEND Total Score[100]

End point description:

ACEND instrument was designed to quantify caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA. The ACEND included a total of seven domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance, and each domain comprised several items. The total score for each domain was calculated on a scale of 0 to 100, with a higher score indicating a decreased caregiver burden. A negative change from baseline indicates an increased caregiver burden. ITT set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[100] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	17		
Units: score on scale				
arithmetic mean (standard deviation)				
Feeding/Grooming/Dressing Total Score	0.6 (± 2.51)	0.8 (± 7.50)		
Sitting/Play Total Score	0.0 (± 11.03)	-2.8 (± 14.48)		
Transfers Total Score	-8.0 (± 12.39)	-2.0 (± 15.34)		
Mobility Total Score	7.1 (± 13.85)	-0.8 (± 15.01)		
Time Total Score	6.3 (± 14.25)	0.4 (± 10.47)		
Emotion Total Score	11.1 (± 7.66)	-2.4 (± 9.44)		
Finance Total Score	15.8 (± 14.29)	-2.4 (± 12.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and C: Number of Participants With WHO Motor Milestones Status

End point title	Parts A and C: Number of Participants With WHO Motor Milestones Status[101]

End point description:

The WHO motor milestones were a set of six milestones in motor development: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone and walking alone. The examiner recorded an overall rating of the participant’s emotional state and then for each milestone one of the following four classifications: no (inability) - child tried but failed to perform the milestone, no (refusal) - child refused to perform despite being calm and alert, yes - child was able to perform the milestone, unable to test - could not be tested because of irritability, drowsiness or sickness. ITT set included all participants who received at least one dose of nusinersen. ‘Number analysed (n)' signifies number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[101] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	37		
Units: motor milestones				
Gain of one or More Motor Milestones	0	3		
No Change	6	32		
Loss of one or More Motor Milestones	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and C: Change From Baseline in PedsQL™ Total Score

End point title	Parts A and C: Change From Baseline in PedsQL™ Total

End point description:

PedsQL was used to measure health related quality of life (HRQOL) in children & adolescents. PedsQL generic core scale included assessment of physical functioning, emotional functioning, social functioning, and school functioning [PedsQL Inventory total score (PQLI)] and PedsQL Neuromuscular Module [Neuromuscular total score (PQLN)] measured HRQOL dimensions specific to with neuromuscular disorders, including SMA. Four dimensions were collected,each item scored on a 5-point ordinal scale (0=Never to 4=Almost Always). Items were reversed scored and were linearly transformed to a 0-100 scale. Total scale score was calculated as sum of all items over number of items answered on all scales. If more than 50% of items or more were missing, scale score was not computed. Higher scores indicated better health related quality of life. ITT set. Subjects analysed: number of participants evaluable for this endpoint. 'Number analysed (n)':number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[102] - 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: Parts A and C arms were planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen	Part C: 50/28 mg Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	14		
Units: score on scale				
arithmetic mean (standard deviation)				
PQLI-Total Score-Subject (n=5,12)	6.1 (± 18.28)	1.1 (± 9.74)		
PQLI-Total Score-Parent (n=5,14)	3.3 (± 12.51)	0.7 (± 8.15)		
PQLN-Total Score-Subject (n=5,12)	9.9 (± 6.94)	6.7 (± 13.11)		
PQLN-Total Score-Parent (n=6,13)	4.7 (± 5.72)	0.1 (± 9.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Change From Baseline in CHOP-INTEND Total Score

End point title	Part C: Change From Baseline in CHOP-INTEND Total Score[103]

End point description:

The CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. It included 16 items (capturing neck, trunk, and proximal and distal limb strength), nine of which were scored 0, 1, 2, 3, or 4, five were scored as 0, 2, or 4, one was scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4 with greater scores indicating greater muscle strength. Total score ranged from 0 (worst possible score) and 64 (best possible score). ITT set included all participants who received at least one dose of nusinersen in the current study. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. Subjects analysed signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[103] - 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: Part C arm was planned to be analysed for this endpoint.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: score on scale				
arithmetic mean (standard deviation)	0.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Change From Baseline in HINE Section 2 Motor Milestones Total Score

End point title	Part C: Change From Baseline in HINE Section 2 Motor Milestones Total Score[104]

End point description:

Section 2 of the HINE was used to assess motor milestones of the participants. Its composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each of these categories, participants can progress from complete absence of a motor ability (the lowest level in each category) through multiple milestones (2 to 4 levels in each category) to the highest level within the category. The 8 categories of HINE Section 2 can be summed to give a total score that ranges from 0 to 26. Safety set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[104] - 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: Part C arm was planned to be analysed for this endpoint.

End point values	Part C: 50/28 mg Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: score on scale				
arithmetic mean (standard deviation)	2.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Participants With Shift From Baseline in PASA Scale Items-Attempted to Drink Liquids and Attempted to Eat Solid Foods

End point title	Part A: Number of Participants With Shift From Baseline in PASA Scale Items-Attempted to Drink Liquids and Attempted to Eat Solid Foods[105]

End point description:

PASA was assessed using a questionnaire. Caregivers were asked a series of questions regarding the mealtime behavior of the participant. The PASA questionnaire was developed to assess the signs and symptoms of dysphagia. It included 33 items across 4 domains that cover general feeding, drinking liquids, eating solid foods, and assessment of swallowing concerns. The 2 items of domains drinking liquids (attempted to drink liquids), eating solid foods (attempted to eat solid foods) were assessed as "Yes"/"No". Data for the 2 items were summarized in terms of the shift from baseline. ITT set included all participants who received at least one dose of nusinersen.

End point type	Secondary

End point timeframe:

Baseline, Day 302

Notes:

[105] - 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: Part A arm was planned to be analysed for this end point.

End point values	Part A: 28/28 Milligrams (mg) Nusinersen			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants				
AttempttoDrinkLiquid:Baseline: No,Postbaseline:Yes	0			
AttempttoDrinkLiquid:Baseline: No, Postbaseline:No	2			
AttempttoDrinkLiquid:Baseline:Yes,Postbaseline:Yes	4			
AttempttoDrinkLiquid:Baseline:Yes,Postbaseline:No	0			
AttempttoEatSolid:Baseline:No,Postbaseline:Yes	0			
AttempttoEatSolid:Baseline:No,Postbaseline:No	0			
AttempttoEatSolid:Baseline:Yes,Postbaseline:Yes	6			
AttempttoEatSolid:Baseline:Yes,Postbaseline:No	0			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Part A: From first dose of the study up to Day 389 Part B: From first dose of the study up to Day 399 Part C: From first dose of the study up to Day 361

Adverse event reporting additional description:

Safety set included all participants who received at least a dose of nusinersen. MedDRA version 24.0 was applied for Part A, MedDRA version 26.1 was applied for Part B, and MedDRA version 26.0 was applied for Part C.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24,26,26.1

Reporting groups

Reporting group title	Part A: Nusinersen 28/28 Milligrams (mg)

Reporting group description:

Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.

Reporting group title	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen

Reporting group description:

Participants with infantile-onset SMA received 4 loading doses of 12 mg of nusinersen intrathecally on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

Reporting group title	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen

Reporting group description:

Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen intrathecally on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

Reporting group title	Part B: Later-Onset SMA: 12/12 mg Nusinersen

Reporting group description:

Participants with later-onset SMA received 4 loading doses of 12 mg of nusinersen intrathecally on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

Reporting group title	Part B: Later-Onset SMA: 50/28 mg Nusinersen

Reporting group description:

Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen intrathecally on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

Reporting group title	Part C: Nusinersen 50/28 mg

Reporting group description:

Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen intrathecally on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.

Serious adverse events	Part A: Nusinersen 28/28 Milligrams (mg)	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	18 / 25 (72.00%)	30 / 50 (60.00%)
number of deaths (all causes)	0	6	10

number of deaths resulting from adverse events	0	6	10
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden infant death syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Organ failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	3 / 25 (12.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Obstructive airways disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
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 acidosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
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 distress			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	4 / 25 (16.00%)	8 / 50 (16.00%)
occurrences causally related to treatment / all	0 / 0	2 / 5	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram qt prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (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
Femur fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (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

Traumatic haemothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy malfunction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Brain stem infarction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Acquired macrocephaly			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Adenoviral upper respiratory infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Covid-19			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis escherichia coli			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human coronavirus OC43 infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			

subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Norovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
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 / 6 (0.00%)	5 / 25 (20.00%)	7 / 50 (14.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Pneumonia acinetobacter			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	7 / 50 (14.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
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 pseudomonal			

subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
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 viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia pneumococcal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: Nusinersen 50/28 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	2 / 16 (12.50%)	6 / 40 (15.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden infant death syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organ failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (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
Aspiration			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (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
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram qt prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Traumatic haemothorax			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy malfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Acquired macrocephaly			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Adenoviral upper respiratory infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis escherichia coli			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human coronavirus OC43 infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Norovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia acinetobacter			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (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
Pneumonia pseudomonal			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 8 (12.50%)	1 / 16 (6.25%)	0 / 40 (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
Pneumonia viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (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
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (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
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part A: Nusinersen 28/28 Milligrams (mg)	Part B: Infantile-Onset SMA: 12/12 mg Nusinersen	Part B: Infantile-Onset SMA: 50/28 mg Nusinersen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	19 / 25 (76.00%)	37 / 50 (74.00%)
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Peripheral coldness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Cyanosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 25 (16.00%)	9 / 50 (18.00%)
occurrences (all)	0	6	12
Vaccination site haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Infusion site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Medical device pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Medical device site discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Vaccination site erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	0
Medical device site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Medical device site hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory complication associated with device			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Mite allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Milk allergy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	5 / 50 (10.00%)
occurrences (all)	0	2	5
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Bronchial obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Respiratory muscle weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Interstitial lung disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Sneezing			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Acute respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory distress			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Increased bronchial secretion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Atelectasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	4
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Decreased bronchial secretion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Dysphoria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Investigations			
CSF pressure increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Crystal urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
CSF protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Body height below normal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Staphylococcus test positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Bacterial test positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Oxygen saturation decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood albumin decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Myocardial necrosis marker			

increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Blood phosphorus increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood creatinine decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Coronavirus test positive			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences (all)	3	0	3
Procedural headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Anaesthetic complication neurological			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2

Procedural vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Post procedural discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	3
Road traffic accident			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Anaesthetic complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Craniocerebral injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Procedural nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Foreign body ingestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Post procedural fever			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Traumatic haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Femur fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1

Periorbital haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Post procedural swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Neurological procedural complication			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Developmental hip dysplasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0

Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Intracranial pressure increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Febrile convulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Bulbar palsy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	3 / 50 (6.00%)
occurrences (all)	0	1	3
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Deficiency anaemia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Hypofibrinogenaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Secondary thrombocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Myopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Eye discharge			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	2 / 25 (8.00%)	4 / 50 (8.00%)
occurrences (all)	2	3	6
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Constipation			

subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	7 / 50 (14.00%)
occurrences (all)	0	2	8
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	5 / 50 (10.00%)
occurrences (all)	0	2	6
Dysbiosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Infantile diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hepatic function abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Dermatitis contact			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Acne infantile			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Eczema infantile			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Dermatitis diaper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Leukocyturia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Muscle contracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Joint contracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Myalgia intercostal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Scoliosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Short stature			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Tendinous contracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Acquired plagiocephaly			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Extremity contracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	3 / 25 (12.00%)	8 / 50 (16.00%)
occurrences (all)	2	3	9
Gingivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	5 / 50 (10.00%)
occurrences (all)	0	2	6

Cystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	3 / 25 (12.00%)	2 / 50 (4.00%)
occurrences (all)	0	3	2
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	3
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Lice infestation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0

Suspected COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Vulvovaginitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Bronchiolitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Pneumonia klebsiella			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Stoma site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	4
Herpangina			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Bronchitis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Cystitis bacterial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1

Enterovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Eye infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Helminthic infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Otitis externa			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pneumonia moraxella			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pneumonia pseudomonal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory tract infection viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Rhinovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Sepsis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Staphylococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Klebsiella urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Klebsiella infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis viral			

subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Acinetobacter infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Enterobacter infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 25 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dairy intolerance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Malnutrition			
subjects affected / exposed	0 / 6 (0.00%)	2 / 25 (8.00%)	5 / 50 (10.00%)
occurrences (all)	0	3	5
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Lactose intolerance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Protein deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Electrolyte imbalance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 25 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Underweight			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Part B: Later-Onset SMA: 12/12 mg Nusinersen	Part B: Later-Onset SMA: 50/28 mg Nusinersen	Part C: Nusinersen 50/28 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	14 / 16 (87.50%)	36 / 40 (90.00%)
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cyanosis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	3 / 40 (7.50%)
occurrences (all)	0	2	3
Vaccination site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Infusion site rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Medical device pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Medical device site discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vaccination site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	10 / 16 (62.50%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Oedema			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Medical device site rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Medical device site hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory complication associated with device			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Mite allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Milk allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	2 / 16 (12.50%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 16 (12.50%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Bronchial obstruction			

subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory muscle weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Acute respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Increased bronchial secretion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Atelectasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Bronchospasm			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Decreased bronchial secretion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Dysphoria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Investigations			
CSF pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Crystal urine present			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 40 (5.00%)
occurrences (all)	0	1	2
CSF protein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Body height below normal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Staphylococcus test positive			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Bacterial test positive			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood creatinine decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Coronavirus test positive			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	3 / 8 (37.50%)	3 / 16 (18.75%)	8 / 40 (20.00%)
occurrences (all)	5	8	12
Procedural headache			
subjects affected / exposed	0 / 8 (0.00%)	4 / 16 (25.00%)	13 / 40 (32.50%)
occurrences (all)	0	7	20
Anaesthetic complication neurological			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	4 / 40 (10.00%)
occurrences (all)	0	1	5
Procedural vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	3 / 40 (7.50%)
occurrences (all)	0	1	4
Post procedural discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
Road traffic accident			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Anaesthetic complication			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Craniocerebral injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Procedural nausea			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Foreign body ingestion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Post procedural fever			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Traumatic haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Periorbital haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Post procedural swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Neurological procedural complication			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Cryptorchism			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Developmental hip dysplasia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	5 / 40 (12.50%)
occurrences (all)	0	0	7
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Disturbance in attention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Dizziness postural			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Intracranial pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tremor			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Febrile convulsion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Bulbar palsy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Deficiency anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hypofibrinogenaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Thrombocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Secondary thrombocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0

Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Eye disorders			
Myopia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Eye discharge			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	2 / 16 (12.50%)	1 / 40 (2.50%)
occurrences (all)	1	2	2
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 16 (12.50%)	1 / 40 (2.50%)
occurrences (all)	0	2	2
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dysbiosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Infantile diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Hepatic function abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Acne infantile			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Eczema infantile			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Leukocyturia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	5
Muscle contracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Osteopenia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Joint contracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 40 (2.50%)
occurrences (all)	0	1	2
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Limb discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Myalgia intercostal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Osteoporosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Scoliosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Short stature			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Tendinous contracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Acquired plagiocephaly			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Extremity contracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	2 / 16 (12.50%)	2 / 40 (5.00%)
occurrences (all)	3	2	3
Gingivitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 16 (12.50%)	0 / 40 (0.00%)
occurrences (all)	1	2	0
COVID-19			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	11 / 40 (27.50%)
occurrences (all)	1	0	12
Cystitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 40 (2.50%)
occurrences (all)	0	1	2
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 40 (5.00%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 16 (12.50%)	4 / 40 (10.00%)
occurrences (all)	0	2	6

Influenza			
subjects affected / exposed	1 / 8 (12.50%)	1 / 16 (6.25%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Lice infestation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Suspected COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Vulvovaginitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Bronchiolitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pneumonia klebsiella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Stoma site infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Herpangina			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Bronchitis viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cystitis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Enterovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Helminthic infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0

Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pneumonia moraxella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Rhinovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Vascular device infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis adenovirus			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Klebsiella urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Klebsiella infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Acinetobacter infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Enterobacter infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dairy intolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Malnutrition			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Lactose intolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Protein deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Electrolyte imbalance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Underweight			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0

Iron deficiency subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 16 (0.00%) 0	0 / 40 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2019	- Clarified that the primary objective for Part B was to examine efficacy, as measured by the change from baseline in CHOP INTEND total score. - Clarified that the remaining assessments that were used to evaluate the clinical efficacy of nusinersen for participants in Part B were secondary endpoints related to a secondary objective. - A separate table for Parts A and C objectives and endpoints was added to emphasize the differences between Part B and Parts A and C, and to clarify that safety was the primary objective for Parts A and C.
05 June 2020	- Made revision to the study stopping rules to clarify that they only apply to the primary safety portions of the study. - The footnotes regarding ECG monitoring in schedule of activities (SoA) tables were revised to adjust the postdose ECG timing and address abnormal ECG results. - The loading dose visit windows for Parts A and B of Study 232SM203 were clarified and revised. - A footnote was added to SoA tables to ensure that efficacy assessments (CHOP INTEND, HFMSE, and RULM) were conducted twice prior to the first dose of study treatment. - Guidance was added on the number of participants with scoliosis and/or severe contractures to be included in Part C of the study. - The study duration was extended, in order to align the requirements of contraception use and reporting, the follow-up period of the study was extended for those participants who require contraception use and an assessment was added on Day 410, Day 420, and Day 382 for Part A, Part B, and Part C, respectively. - Inclusion and exclusion criteria was updated. - A new section was added to the protocol to provide additional details on ventilation use.
05 August 2020	- Made revision to the study stopping rules so that they apply to all participants in Parts A and B of the study. - Language was added to the protocol regarding remote monitoring of study sites during the global coronavirus disease (COVID-19) pandemic.
01 October 2021	- Increased the sample size by including an additional cohort of up to approximately 20 adult participants in Part C to allow collection of clinical data in adults transitioning from the currently approved nusinersen dosing regimen to a higher dose. - The timepoints for collection of vital signs, neurological examinations, and ECGs and the collection windows for plasma PK samples were updated for Parts B and C. - A schedule of activities table specifically for Part C Cohort 2 was added. - A new table was added for participants in Part B who discontinued study treatment but agreed to remain in the study for follow-up. - Inclusion and exclusion criteria was updated for Parts A,B and C. - Added details on contracture assessment, to update the information on PedsQL for the adult participants who enrolled in Cohort 2 of Part C. - Updated growth parameters to allow for measurement of length for participants with later-onset SMA who were not able to have height measured.

05 May 2022	- Reduced the sample size for Part B infantile onset participants to 75. As a result, the total sample size for the study was adjusted to 145 participants. - Part B exclusion criteria was updated. - The PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module for participants ≥ 26 years of age were added. - Language was updated in laboratory safety assessments to further specify that total protein would be measured for the CSF local laboratory sample. - All references to an interim analysis being performed to assess the feasibility of borrowing participant data from Study CS3B were removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported