



Clinical trial results:

An Open-Label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

Summary

EudraCT number	2014-002098-12
Trial protocol	IT GB DE
Global end of trial date	16 December 2024

Results information

Result version number	v1
This version publication date	29 June 2025
First version publication date	29 June 2025

Trial information

Trial identification

Sponsor protocol code	232SM201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02386553
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)	Yes
EMA paediatric investigation plan number(s)	EMA-001448-PIP01-13
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	16 December 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to examine the efficacy of multiple doses of ISIS 396443 administered intrathecally in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic spinal muscular atrophy (SMA).

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	18 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Qatar: 1
Worldwide total number of subjects	25
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	21
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at the investigative sites in Australia, Germany, Italy, Qatar, Taiwan, Turkey and the United States from 18 May 2015 to 17 Dec 2024.

Pre-assignment

Screening details:

A total of 25 participants diagnosed with Spinal Muscular Atrophy (SMA) were enrolled in the study of which 22 participants completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ISIS 396443 2 SMN2 Copies

Arm description:

Participants with 2 survival motor neuron 2 (SMN2) copies received 12 milligrams (mg) nusinersen, intrathecally (IT) on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.

Arm type	Experimental
Investigational medicinal product name	Nusinersen
Investigational medicinal product code	ISIS 396443
Other name	BIIB058, Spinraza™
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	ISIS 396443 3 SMN2 Copies
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Arm description:

Participants with 3 SMN2 copies received 12 mg nusinersen, IT on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.

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Routes of administration	Intrathecal use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies
Started	15	10
Completed	13	9
Not completed	2	1
Reason Not Specified	1	1
Withdrawal by parent/Guardian	1	-

Baseline characteristics

Reporting groups

Reporting group title	ISIS 396443 2 SMN2 Copies
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Reporting group description:

Participants with 2 survival motor neuron 2 (SMN2) copies received 12 milligrams (mg) nusinersen, intrathecally (IT) on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.

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Reporting group values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies	Total
Number of subjects	15	10	25
Age Categorical Units: Subjects			

Age continuous			
The Intent-to-treat (ITT) set included all participants who received at least 1 dose of ISIS 396443.			
Units: days			
arithmetic mean	19.5	22.3	
standard deviation	± 9.29	± 12.45	-
Gender categorical			
Units: Subjects			
Male	8	4	12
Female	7	6	13
Race			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	1	2	3
White	8	6	14
Other	2	1	3
Not Reported	3	1	4
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	10	9	19
Not Reported	3	1	4

End points

End points reporting groups

Reporting group title	ISIS 396443 2 SMN2 Copies
Reporting group description: Participants with 2 survival motor neuron 2 (SMN2) copies received 12 milligrams (mg) nusinersen, intrathecally (IT) on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.	
Reporting group title	ISIS 396443 3 SMN2 Copies
Reporting group description: Participants with 3 SMN2 copies received 12 mg nusinersen, IT on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.	

Primary: Time to Death or Respiratory Intervention

End point title	Time to Death or Respiratory Intervention ^[1]
End point description: The time was the age of the participant at the first occurrence of either a respiratory intervention or death. Respiratory intervention was defined as invasive or noninvasive ventilation for ≥6 hours/day continuously for 7 or more days OR tracheostomy. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here, 'number of subjects analysed' signifies the number of participants analysed in this endpoint. 99999 indicates that median and upper range of 95% CI was not estimable due to low number of events of permanent ventilation or death.	
End point type	Primary
End point timeframe: Screening up to Day 2891	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned to be analysed.	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	0 ^[2]		
Units: months				
median (confidence interval 95%)	99999 (19.1 to 99999)	(to)		

Notes:
[2] - 'Number of subjects analysed' signifies the number of participants analysed in this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Developing Clinically Manifested Spinal Muscular Atrophy (SMA)

End point title	Proportion of Participants Developing Clinically Manifested Spinal Muscular Atrophy (SMA)
End point description: A participant was considered having clinically manifested SMA if any of the following occurred: <ul style="list-style-type: none">Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles	

(3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support

- Failure to achieve the ability to sit without support
- Failure to achieve standing with assistance
- Failure to achieve hands-and-knees crawling
- Failure to achieve walking with assistance by 24 months of age
- Failure to achieve standing alone by 24 months of age
- Failure to achieve walking alone by 24 months of age

The ITT set included all participants who received at least 1 dose of ISIS 396443.

End point type	Secondary
End point timeframe:	
At 13 and 24 months of age	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Proportion of participants				
number (confidence interval 95%)				
13 months of age	0.67 (0.39 to 0.87)	0.20 (0.04 to 0.56)		
24 months of age	0.47 (0.22 to 0.73)	0 (0.00 to 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive

End point title	Percentage of Participants Alive
End point description:	
A Kaplan-Meier survival curve was used to estimate the proportion of subjects alive at 13 months and 2, 3, 4, 5, 6, 7, and 8 years of age. The ITT set included all participants who received at least 1 dose of ISIS 396443.	
End point type	Secondary
End point timeframe:	
At 13 months, and 2, 3, 4, 5, 6, 7 and 8 years of age	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: percentage of participants				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Attained Motor Milestones Assessed as Part of the Hammersmith Infant Neurological Examination (HINE)

End point title	Percentage of Participants Who Attained Motor Milestones Assessed as Part of the Hammersmith Infant Neurological Examination (HINE)
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End point description:

HINE is evaluated in infants between 2-24 months of age. It's a simple, standardized instrument including 26 items assessing different aspects of neurological examinations, such as cranial nerves, posture, movements, tone, and reflexes. In this study, Module 2 of HINE (HINE-2) was assessed, which evaluates 8 developmental milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) scored on a 3, 4, or 5-point scale, with 0 indicating inability to perform task and score of 2, 3, or 4 indicating full milestone development. Total score is calculated by summing item scores to give maximum possible score of 26. Higher score indicates good neurological function. The ITT set included all participants who received at least 1 dose of ISIS 396443.

End point type	Secondary
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End point timeframe:

Day 700

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: percentage of participants				
number (not applicable)				
Sitting: Stable Sit or Pivots (Rotates)	100	100		
Standing: Stands With Support or Stands Unaided	93	100		
Standing: Stands Unaided	73	100		
Walking: Walks Holding on/Walking Independently	87	100		
Walking: Walking Independently	67	100		
Head Control: All the Time Maintained Upright	100	100		
Voluntary Grasp: Pincer Grasp	100	100		
Ability to Kick: Touches Toe	100	100		
Rolling: Prone to Supine or Supine to Prone	100	100		
Crawling: Crawling on Hands and Knees	73	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Attained Motor Milestones as Assessed by World Health Organization (WHO) Criteria

End point title	Percentage of Participants Who Attained Motor Milestones as Assessed by World Health Organization (WHO) Criteria
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End point description:

The WHO motor milestones are a set of six milestones in motor development, all of which would be expected to be attained by 24 months of age in healthy children. The individual milestones are: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone and walking alone. The ITT set included all participants who received at least 1 dose of ISIS 396443.

End point type	Secondary
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End point timeframe:

Baseline up to Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: percentage of participants				
number (not applicable)				
First Sitting Without Support	100	100		
First Hands-and-Knees Crawling	93	100		
First Standing With Assistance	100	100		
First Walking With Assistance	93	100		
First Standing Alone	93	100		
First Walking Alone	87	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) Motor Function Scale

End point title	Change From Baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) Motor Function Scale
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End point description:

CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. Participants who were ≥ 2 years were continued to be assessed until CHOP INTEND maximum score of 64 was achieved. 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 higher scores indicating greater muscle strength and function. Total score was calculated as sum of scores for each item. Total score ranged from 0 (worst possible score) and 64 (best possible score). Assessments were discontinued once participants achieved maximum score of 64, so number of participants with available data points decreased over time. ITT set included all participants who received at least 1 dose of ISIS 396443. 'n' signifies number of participants available for analysis at specified time point. 9999 indicates that data was not evaluable at given time

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	47.0 (± 10.04)	51.9 (± 6.10)		
Change at Day 2891 (n= 2, 0)	29.0 (± 11.31)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE)

End point title	Change From Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE)
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End point description:

The HFMSE consists of 33 scored activities used to assess motor function in children with SMA. Participants were asked to do a specific activity (such as rolling) and they were then graded on the quality and execution of that movement on a scale of 0=being unable, 1=performed with some compensation, and 2=unaided. The overall score is the sum of the scores for all activities with a maximum achievable score of 66. Higher scores indicate increased motor function. Baseline was defined as the time of first HFMSE score after Day 700. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point. 9999 indicates that data was not evaluable at given time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 2160

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	34.5 (± 12.15)	46.4 (± 7.44)		
Change at Day 2160 (n= 10, 6)	23.5 (± 5.34)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight for Age

End point title	Change From Baseline in Weight for Age
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End point description:

The World Health Organization (WHO) child growth standards for participants aged up to 10 years was

used to determine the percentiles. WHO Anthro software was used to calculate the percentiles for the given weights of each child. Negative change from baseline indicates low weight for age percentile. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point.

End point type	Secondary
End point timeframe:	
Baseline, Day 2891	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: percentile				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	44.04 (± 31.197)	34.76 (± 16.054)		
Change at Day 2891 (n= 13, 9)	-1.46 (± 48.041)	24.49 (± 40.263)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight for Length

End point title	Change From Baseline in Weight for Length
End point description:	
<p>The World Health Organization (WHO) child growth standards for participants aged up to 10 years was used to determine the percentiles. WHO Anthro software was used to calculate the percentiles for the given weights of each child. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point. 9999 indicates that data was not evaluable at given time point. 999999 indicates that since only one participant was evaluable at Day 2891, the standard deviation (SD) could not be estimated.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Day 1849	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: percentile				
arithmetic mean (standard deviation)				
Baseline (n= 10, 6)	21.63 (± 22.806)	45.26 (± 28.039)		
Change at Day 1849	38.94 (± 999999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Head Circumference

End point title	Change From Baseline in Head Circumference
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End point description:

The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point. 9999 indicates that data was not evaluable at given time point. 999999 indicates that since only one participant was evaluable at Day 2891, the SD could not be estimated.

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	35.59 (± 2.285)	36.11 (± 2.198)		
Change at Day 2891 (n= 0, 1)	9999 (± 9999)	19.00 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Chest Circumference

End point title	Change From Baseline in Chest Circumference
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End point description:

The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point. 9999 indicates that data was not evaluable at given time point. 999999 indicates that since only one participant was evaluable at Day 2891, the SD could not be estimated.

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	34.43 (± 2.724)	35.25 (± 2.551)		
Change at Day 2891 (n= 0, 1)	9999 (± 9999)	28.20 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Head to Chest Circumference Ratio

End point title	Change from Baseline in Head to Chest Circumference Ratio
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End point description:

Negative change from baseline indicates reduction in head-to-chest circumference ratio. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point. 9999 indicates that data was not evaluable at given time point. 999999 indicates that since only one participant was evaluable at Day 2891, the SD could not be estimated.

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	1.036 (± 0.0537)	1.027 (± 0.0595)		
Change at Day 2891 (n= 0, 1)	9999 (± 9999)	-0.186 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Arm Circumference

End point title	Change From Baseline in Arm Circumference
End point description: The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point. 9999 indicates that data was not evaluable at given time point. 999999 indicates that since only one participant was evaluable at Day 2891, the SD could not be estimated.	
End point type	Secondary
End point timeframe: Baseline, Day 2891	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	10.85 (± 1.251)	10.77 (± 1.656)		
Change at Day 2891 (n= 0, 1)	9999 (± 9999)	9.40 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)
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. The ITT set included all participants who received at least 1 dose of ISIS 396443.	
End point type	Secondary
End point timeframe: From first dose of study drug up to end of study (up to 2891 days)	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: participants				
TEAEs	15	10		
SAEs	10	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Hematology Parameters)

End point title	Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Hematology Parameters)
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End point description:

Hematology parameters included hemoglobin, hematocrit, erythrocytes, platelets, leukocytes, neutrophils, eosinophils, basophils, lymphocytes, and monocytes count. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available. Here, shift to low indicated 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 values. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis of the specified hematology parameter.

End point type	Secondary
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End point timeframe:

Baseline up to Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: participants				
Hemoglobin Shift to Low (n= 13, 10)	10	5		
Hemoglobin Shift to High (n= 13, 9)	3	4		
Hematocrit Shift to High (n= 11, 10)	7	7		
Hematocrit Shift to High (n= 13, 9)	4	4		
Erythrocytes Shift to Low (n= 14, 9)	3	5		
Erythrocytes Shift to High (n= 13, 9)	9	3		
Leukocytes Shift to Low (n= 13, 10)	5	6		
Leukocytes Shift to High (n= 15, 9)	11	4		
Neutrophils/Leukocytes Shift to Low (n= 9, 4)	4	2		
Neutrophils/Leukocytes Shift to High (n= 9, 4)	4	0		
Eosinophils/Leukocytes Shift to Low (n= 15, 10)	0	0		
Eosinophils/Leukocytes Shift to High (n= 8, 9))	7	8		

Basophils/Leukocytes Shift to Low (n= 14, 10)	0	0		
Basophils/Leukocytes Shift to High (n= 13, 10)	10	9		
Lymphocytes/Leukocytes Shift to Low (15, 10)	4	1		
Lymphocytes/Leukocytes Shift to High (n= 6, 4)	6	4		
Monocytes/Leukocytes Shift to Low (n= 14, 10)	11	7		
Monocytes/Leukocytes Shift to High (n= 12, 6)	4	1		
Neutrophils Shift to Low (n= 9, 4)	2	1		
Neutrophils Shift to High (n= 9, 4)	3	0		
Neutrophils, Segmented Shift to Low (n= 15, 10)	6	4		
Neutrophils, Segmented Shift to High (n= 15, 10)	9	1		
Eosinophils Shift to Low (n= 15, 10)	0	0		
Eosinophils Shift to High (n= 11, 8)	11	8		
Basophils Shift to Low (n= 15, 9)	0	0		
Basophils Shift to High (n= 14, 10)	4	2		
Lymphocytes Shift to Low (n= 15, 10)	2	1		
Lymphocytes Shift to High (n= 14, 8)	11	8		
Monocytes Shift to Low (n= 15, 10)	14	10		
Monocytes Shift to High (n= 14, 6)	4	0		
Platelets Shift to Low (n= 15, 10)	3	5		
Platelets Shift to High (n= 10, 8)	9	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)

End point title	Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)
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End point description:

Blood chemistry parameters included bilirubin (direct and indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, creatinine, sodium, potassium, chloride, protein, albumin, calcium, phosphate, glucose, cystatin C, creatine kinase. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available. Here, shift to low indicated 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 values. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis of the specified blood chemistry parameter.

End point type	Secondary
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End point timeframe:

Baseline up to Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: participants				
Bilirubin Shift to Low (n= 14, 10)	14	10		
Bilirubin Shift to High (n= 9, 6)	2	1		
Indirect Bilirubin Shift to Low (n= 15, 10)	0	0		
Indirect Bilirubin Shift to High (n= 8, 6)	1	1		
Direct Bilirubin Shift to Low (n= 14, 10)	14	6		
Direct Bilirubin Shift to High (n= 13, 9)	0	1		
Alkaline Phosphatase Shift to Low (n= 15, 10)	3	0		
Alkaline Phosphatase Shift to High (n= 15, 9)	2	5		
Alanine Aminotransferase Shift to Low (n= 15, 10)	0	0		
Alanine Aminotransferase Shift to High (n= 14, 7)	7	2		
Aspartate Aminotransferase Shift to Low (n=15,10)	0	0		
Aspartate Aminotransferase Shift to High (n=14,8)	6	2		
Gamma Glutamyl Transferase Shift to Low (n=15,10)	1	0		
Gamma Glutamyl Transferase Shift to High(n=15,10)	1	0		
Urea Nitrogen Shift to Low (n= 15, 8)	6	0		
Urea Nitrogen Shift to High (n= 15, 10)	0	2		
Creatinine Shift to Low (n= 11, 7)	5	2		
Creatinine Shift to High (n= 15, 10)	1	4		
Sodium Shift to Low (n= 13, 10)	2	0		
Sodium Shift to High (n= 15, 10)	0	1		
Potassium Shift to Low (n= 15, 10)	0	1		
Potassium Shift to High (n= 13, 7)	8	3		
Chloride Shift to Low (n= 15, 10)	0	1		
Chloride Shift to High (n= 15, 10)	0	2		
Protein Shift to Low (n= 11, 8)	2	5		
Protein Shift to High (n= 15, 10)	13	6		
Albumin Shift to Low (n= 15, 9)	0	0		
Albumin Shift to High (n= 14, 9)	10	8		
Bicarbonate Shift to Low (n= 14, 10)	8	7		
Bicarbonate Shift to High (n= 15, 10)	1	0		
Calcium Shift to Low (n= 15, 10)	3	3		
Calcium Shift to High (n= 10, 9)	6	8		
Phosphate Shift to Low (n= 15, 10)	0	0		
Phosphate Shift to High (n= 15, 9)	9	4		
Glucose Shift to Low (n= 14, 10)	7	6		
Glucose Shift to High (n= 12, 8)	11	7		
Cystatin C Shift to Low (n= 15, 9)	6	4		
Cystatin C Shift to High (n= 15, 9)	2	0		
Creatine Kinase Shift to Low (n= 15, 10)	0	0		
Creatine Kinase Shift to High (n= 9, 7)	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Urinalysis Parameters)

End point title	Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Urinalysis Parameters)
End point description:	
<p>Urinalysis included assessments of specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, erythrocytes, leukocytes, 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. Here, shift to low indicated 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 values. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis of the specified urinalysis parameter.</p>	
End point type	Secondary
End point timeframe:	
Baseline up to Day 2891	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: participants				
Specific Gravity Shift to Low (n= 13, 8)	3	1		
Specific Gravity Shift to High (n= 15, 10)	6	5		
pH Shift to Low (n= 14, 10)	0	1		
pH Shift to High (n= 15, 9)	3	3		
Protein Shift to High/positive (n= 14, 9)	13	8		
Glucose Shift to High/positive (n= 15, 10)	1	0		
Ketones Shift to High/positive (n= 15, 10)	9	6		
Bilirubin Shift to High/positive (n= 15, 10)	0	0		
Occult Blood Shift to High/positive (n= 15, 9)	4	2		
Erythrocytes Shift to High/positive (n= 15, 10)	7	1		
Leukocytes Shift to High/positive (n= 12, 10)	5	4		
Epithelial Cells Shift to High/positive (n= 8, 3)	5	0		
Bacteria Shift to High/positive (n= 7, 7)	7	6		
Casts Shift to High/positive (n= 3, 3)	1	2		

Crystals Shift to High/positive (n= 2, 3)	1	2		
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline in Coagulation Parameters [Activated Partial Thromboplastin Time (aPTT)]

End point title	Number of Participants With Shifts From Baseline in Coagulation Parameters [Activated Partial Thromboplastin Time (aPTT)]
End point description: aPTT was evaluated to assess safety. Shift to high measured change in normal, low and unknown values at baseline to high values postbaseline. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here, 'number of subjects analysed' signifies the number of participants analysed in this endpoint.	
End point type	Secondary
End point timeframe: Baseline up to Day 2891	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: participants	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline in Coagulation Parameters [Prothrombin Time (PT)]

End point title	Number of Participants With Shifts From Baseline in Coagulation Parameters [Prothrombin Time (PT)]
End point description: PT was evaluated to assess safety. Shift to high measured change in normal, low and unknown values at baseline to high values postbaseline. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here, 'number of subjects analysed' signifies the number of participants analysed in this endpoint.	
End point type	Secondary
End point timeframe: Baseline up to Day 2891	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: participants	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs (Temperature)

End point title	Change From Baseline in Vital Signs (Temperature)
End point description:	
Negative change from baseline indicates reduction in temperature. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point.	
End point type	Secondary
End point timeframe:	
Baseline, Day 2891	

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: celsius				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	36.7 (± 0.39)	36.8 (± 0.44)		
Change at Day 2891 (n= 14, 9)	0.0 (± 0.54)	-0.1 (± 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinically Significant Shifts in Electrocardiograms (ECG) Abnormalities

End point title	Percentage of Participants With Clinically Significant Shifts in Electrocardiograms (ECG) Abnormalities
End point description:	
Clinical significance of abnormalities in ECG was determined based on the investigator's discretion. Shift to abnormal indicated values that were normal or unknown at baseline and shifted to abnormal values post-baseline. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here, 'number of subjects analysed' signifies the number of participants analysed in this endpoint.	
End point type	Secondary

End point timeframe:
Baseline up to Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: percentage of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline in Coagulation Parameters [International Normalized Ratio (INR)]

End point title	Number of Participants With Shifts From Baseline in Coagulation Parameters [International Normalized Ratio (INR)]
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End point description:

INR was evaluated to assess safety. Shift to high measured change in normal, low and unknown values at baseline to high values postbaseline. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here, 'number of subjects analysed' signifies the number of participants analysed in this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: participants	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs [Blood Pressure (BP)]

End point title	Change From Baseline in Vital Signs [Blood Pressure (BP)]
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End point description:

The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline-Systolic BP (n= 15, 10)	83.4 (± 16.40)	88.1 (± 17.84)		
Change at Day 2891-Systolic BP (n=14,9)	22.9 (± 15.29)	13.6 (± 15.24)		
Baseline-Diastolic BP (n= 15, 10)	51.1 (± 17.46)	50.8 (± 12.30)		
Change at Day 2891-Diastolic BP (n=14,9)	12.8 (± 17.16)	11.0 (± 13.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs (Heart Rate)

End point title	Change From Baseline in Vital Signs (Heart Rate)
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End point description:

Negative change from baseline indicates reduction in heart rate. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here, 'number of subjects analysed' signifies the number of participants analysed in this endpoint. Here 'n' signifies the number of participants available for analysis at a specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	9		
Units: beats per minute (beats/min)				
arithmetic mean (standard deviation)				
Baseline (n= 15, 9)	141.5 (± 14.71)	154.2 (± 16.55)		
Change at Day 2891 (n= 14, 8)	-47.2 (± 20.86)	-62.4 (± 25.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs (Respiratory Rate)

End point title	Change From Baseline in Vital Signs (Respiratory Rate)
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End point description:

Negative change from baseline indicates reduction in respiratory rate. The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 2891

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: breaths per minute (breaths/min)				
arithmetic mean (standard deviation)				
Baseline (n= 15, 10)	42.1 (± 12.17)	39.8 (± 13.87)		
Change at Day 2891 (n= 14, 9)	-21.0 (± 12.39)	-20.6 (± 14.43)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Neurological Examination Abnormalities Reported as AEs
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End point description:

Participants with abnormalities in neurological examinations recorded as AEs were reported. The ITT set included all participants who received at least 1 dose of ISIS 396443.

End point type	Secondary
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End point timeframe:

From first dose of study drug up to end of study (up to 2891 days)

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: participants				
Muscle contractions involuntary	8	1		
Dysarthria	7	1		
Tremor	8	0		

Hypotonia	4	0		
Areflexia	2	1		
Facial paresis	2	0		
Hyperreflexia	1	1		
Myoclonus	2	0		
Clonus	1	0		
Extensor plantar response	1	0		
Peripheral sensory neuropathy	1	0		
Unresponsive to stimuli	1	0		
Muscular weakness	9	1		
Torticollis	1	1		
Muscle spasms	0	1		
Muscle twitching	0	1		
Trismus	1	0		
Winged scapula	1	0		
Anisocoria	0	1		
Heterophoria	1	0		
Strabismus	0	1		
Vision blurred	0	1		
Automatism	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal fluid (CSF) Concentration of Nusinersen

End point title	Cerebrospinal fluid (CSF) Concentration of Nusinersen
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End point description:

The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point.

End point type	Secondary
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End point timeframe:

Predose on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, 2801

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1, Pre-dose (n= 14, 9)	0.03 (± 0.00)	0.03 (± 0.00)		
Day 15, Pre-dose (n= 14, 10)	7.52 (± 189.00)	10.22 (± 285.47)		
Day 29, Pre-dose (n= 14, 10)	23.41 (± 72.04)	24.56 (± 85.78)		
Day 64, Pre-dose (n= 12, 9)	14.95 (± 58.06)	21.33 (± 63.00)		

Day 183, Pre-dose (n= 14, 9)	11.66 (± 69.60)	13.85 (± 54.32)		
Day 302, Pre-dose (n= 15, 10)	11.34 (± 54.67)	10.06 (± 27.29)		
Day 421, Pre-dose (n= 13, 10)	12.20 (± 66.72)	10.53 (± 67.48)		
Day 540, Pre-dose (n= 15, 9)	10.23 (± 38.84)	9.42 (± 51.04)		
Day 659, Pre-dose (n= 14, 10)	11.91 (± 42.32)	10.30 (± 38.34)		
Day 778, Pre-dose (n= 14, 10)	10.87 (± 54.28)	11.77 (± 61.01)		
Day 897, Pre-dose (n= 15, 10)	11.03 (± 43.91)	10.72 (± 35.90)		
Day 1016, Pre-dose (n= 15, 9)	12.06 (± 58.41)	10.65 (± 39.34)		
Day 1135, Pre-dose (n= 15, 10)	10.49 (± 46.05)	10.87 (± 36.62)		
Day 1254, Pre-dose (n= 15, 9)	12.88 (± 47.06)	11.29 (± 33.29)		
Day 1373, Pre-dose (n= 14, 10)	11.94 (± 61.51)	10.19 (± 52.12)		
Day 1492, Pre-dose (n= 14, 8)	15.04 (± 51.20)	12.71 (± 92.23)		
Day 1611, Pre-dose (n= 13, 8)	13.46 (± 40.19)	13.90 (± 36.31)		
Day 1730, Pre-dose (n= 9, 9)	13.63 (± 57.76)	15.14 (± 42.12)		
Day 1849, Pre-dose (n= 11, 9)	15.14 (± 63.15)	14.19 (± 42.87)		
Day 1968, Pre-dose (n= 10, 8)	16.52 (± 67.05)	17.46 (± 48.67)		
Day 2087, Pre-dose (n= 12, 10)	15.57 (± 47.34)	17.07 (± 58.91)		
Day 2206, Pre-dose (n= 13, 9)	16.95 (± 45.86)	17.16 (± 46.34)		
Day 2325, Pre-dose (n= 12, 8)	18.27 (± 59.23)	20.02 (± 37.41)		
Day 2444, Pre-dose (n= 13, 9)	16.92 (± 49.19)	17.01 (± 40.87)		
Day 2563, Pre-dose (n= 12, 9)	16.74 (± 53.14)	13.37 (± 85.72)		
Day 2682, Pre-dose (n= 11, 9)	17.42 (± 44.34)	16.05 (± 41.83)		
Day 2801, Pre-dose (n= 13, 9)	17.44 (± 45.60)	17.85 (± 36.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Nusinersen

End point title	Plasma Concentration of Nusinersen
End point description:	
The ITT set included all participants who received at least 1 dose of ISIS 396443. Here 'n' signifies the number of participants available for analysis at a specified time point.	
End point type	Secondary

End point timeframe:

Predose on Days 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, 2801 and 4-hour post-dose on Day 1

End point values	ISIS 396443 2 SMN2 Copies	ISIS 396443 3 SMN2 Copies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: ng/ml				
geometric mean (geometric coefficient of variation)				
Day 1, 4 hours post-dose (n= 12, 9)	391.66 (± 113.16)	406.69 (± 82.92)		
Day 64, Pre-dose (n= 15, 10)	1.60 (± 34.52)	1.56 (± 46.54)		
Day 183, Pre-dose (n= 13, 10)	0.73 (± 27.03)	0.81 (± 19.82)		
Day 302, Pre-dose (n= 14, 9)	0.82 (± 54.28)	0.81 (± 21.12)		
Day 421, Pre-dose (n= 15, 10)	0.78 (± 39.94)	0.82 (± 29.31)		
Day 540, Pre-dose (n= 15, 9)	0.72 (± 29.72)	0.72 (± 19.16)		
Day 659, Pre-dose (n= 15, 10)	0.74 (± 26.78)	0.78 (± 32.51)		
Day 778, Pre-dose (n= 15, 10)	0.68 (± 48.37)	0.81 (± 23.52)		
Day 897, Pre-dose (n= 15, 10)	0.71 (± 34.77)	0.63 (± 40.31)		
Day 1016, Pre-dose (n= 15, 10)	0.69 (± 38.47)	0.74 (± 21.97)		
Day 1135, Pre-dose (n= 13, 10)	0.67 (± 33.70)	0.58 (± 33.78)		
Day 1254, Pre-dose (n= 15, 8)	0.63 (± 27.16)	0.60 (± 24.10)		
Day 1373, Pre-dose (n= 15, 10)	0.60 (± 39.79)	0.59 (± 17.98)		
Day 1492, Pre-dose (n= 14, 7)	0.69 (± 40.55)	0.68 (± 43.50)		
Day 1611, Pre-dose (n= 13, 7)	0.62 (± 38.14)	0.53 (± 43.12)		
Day 1730, Pre-dose (n= 8, 9)	0.54 (± 16.13)	0.53 (± 30.84)		
Day 1849, Pre-dose (n= 9, 9)	0.47 (± 52.05)	0.49 (± 36.37)		
Day 1968, Pre-dose (n= 10, 8)	0.53 (± 25.66)	0.43 (± 22.96)		
Day 2087, Pre-dose (n= 14, 9)	0.55 (± 40.43)	0.47 (± 31.50)		
Day 2206, Pre-dose (n= 14, 9)	0.43 (± 43.01)	0.40 (± 32.58)		
Day 2325, Pre-dose (n= 12, 9)	0.46 (± 56.98)	0.45 (± 35.19)		
Day 2444, Pre-dose (n= 13, 9)	0.43 (± 35.15)	0.51 (± 17.26)		
Day 2563, Pre-dose (n= 13, 9)	0.38 (± 61.73)	0.42 (± 31.10)		
Day 2682, Pre-dose (n= 12, 9)	0.36 (± 55.66)	0.40 (± 24.48)		
Day 2801, Pre-dose (n= 13, 9)	0.39 (± 36.16)	0.35 (± 65.12)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of the informed consent form (ICF) up to the end of the study (up to Day 2891)

Adverse event reporting additional description:

The ITT set included all participants who received at least 1 dose of ISIS 396443.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	ISIS 396443 3 SMN2 copies
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Reporting group description:

Participants with 3 SMN2 copies received 12 mg nusinersen, IT on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.

Reporting group title	ISIS 396443 2 SMN2 copies
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Reporting group description:

Participants with 2 SMN2 copies received 12 mg nusinersen, IT on Days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778, 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801.

Serious adverse events	ISIS 396443 3 SMN2 copies	ISIS 396443 2 SMN2 copies	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	10 / 15 (66.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Respirovirus test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza a virus test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device change			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hyperreflexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Tendon disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	5 / 15 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia bacterial			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Feeding disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ISIS 396443 3 SMN2 copies	ISIS 396443 2 SMN2 copies	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	15 / 15 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Vascular disorders Hypertension subjects affected / exposed occurrences (all) Aortic dilatation subjects affected / exposed occurrences (all) Pallor subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Pregnancy, puerperium and perinatal conditions Umbilical granuloma subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Infusion site bruising subjects affected / exposed occurrences (all) Gait disturbance subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Catheter site pain subjects affected / exposed occurrences (all) Application site erythema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 2 / 10 (20.00%) 3 2 / 10 (20.00%) 2 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 4 / 15 (26.67%) 4 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1	

Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Medical device site rash subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Pyrexia subjects affected / exposed occurrences (all)	8 / 10 (80.00%) 40	14 / 15 (93.33%) 78	
Malaise subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 2	
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Anaphylactic reaction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Dust allergy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 15 (0.00%) 0	
Food allergy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 3	
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 15 (13.33%) 2	
Immunodeficiency			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Multiple allergies subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Seasonal allergy subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 4	3 / 15 (20.00%) 3	
Reproductive system and breast disorders Vulvovaginal rash subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 1	
Respiratory, thoracic and mediastinal disorders Aspiration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Asthma subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 15 (20.00%) 4	
Adenoidal hypertrophy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Atelectasis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Bronchial hyperreactivity subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Bronchitis chronic subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2	
Bronchospasm subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Catarrh			

subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Choking		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Cough		
subjects affected / exposed	7 / 10 (70.00%)	11 / 15 (73.33%)
occurrences (all)	30	31
Cyanosis central		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Dysphonia		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Dyspnoea		
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	4
Epistaxis		
subjects affected / exposed	4 / 10 (40.00%)	0 / 15 (0.00%)
occurrences (all)	4	0
Hypoxia		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Increased bronchial secretion		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	2
Acute respiratory failure		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	2
Lower respiratory tract congestion		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Increased upper airway secretion		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Rhinitis allergic		

subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)
occurrences (all)	3	1
Respiratory muscle weakness		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Respiratory distress		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Respiratory disorder		
subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)
occurrences (all)	6	4
Respiratory acidosis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Pulmonary artery dilatation		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Productive cough		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	3
Pneumonitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Pharyngeal erythema		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Oropharyngeal pain		
subjects affected / exposed	3 / 10 (30.00%)	4 / 15 (26.67%)
occurrences (all)	4	5
Obstructive sleep apnoea syndrome		
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)
occurrences (all)	1	4
Lower respiratory tract inflammation		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Nasal congestion		

subjects affected / exposed	4 / 10 (40.00%)	5 / 15 (33.33%)	
occurrences (all)	7	12	
Nasal septum deviation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Stridor			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sputum retention			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	5 / 10 (50.00%)	7 / 15 (46.67%)	
occurrences (all)	21	16	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Upper respiratory tract congestion			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Wheezing			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Upper-airway cough syndrome			
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Procedural anxiety			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Disturbance in social behaviour			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Automatism			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Autism spectrum disorder			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Investigations			
Adenovirus test positive			
subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Audiogram abnormal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Blood calcium increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood glucose decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Blood iron decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Body temperature increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Bone density decreased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	2
Enterovirus test positive		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
C-reactive protein increased		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	3
Candida test positive		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Carnitine decreased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Crystal urine present		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Cystatin c increased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Breath sounds abnormal		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Eosinophil count increased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Haemoglobin decreased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Heart rate increased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Human rhinovirus test positive		
subjects affected / exposed	3 / 10 (30.00%)	1 / 15 (6.67%)
occurrences (all)	3	1
Lymphocyte count increased		

subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Nerve conduction studies abnormal		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Streptococcus test positive		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Oxygen saturation decreased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Platelet count increased		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	2
Protein urine present		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Respirovirus test positive		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Sars-cov-2 test positive		
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)
occurrences (all)	1	2
Serratia test positive		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Neutrophil count increased		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
White blood cell count increased		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Weight decreased		
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)
occurrences (all)	1	2
Weight increased		

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Walking distance test abnormal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Musculoskeletal procedural complication			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Nail injury			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Lip injury			
subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 15 (6.67%) 1	
Ligament sprain			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Nasal injury			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Foreign body in respiratory tract			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 1	
Fall			
subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 12	8 / 15 (53.33%) 12	
Contusion			
subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	4 / 15 (26.67%) 4	
Arthropod sting			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Arthropod bite		
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)
occurrences (all)	1	5
Humerus fracture		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Subcutaneous haematoma		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Post lumbar puncture syndrome		
subjects affected / exposed	4 / 10 (40.00%)	2 / 15 (13.33%)
occurrences (all)	9	3
Post procedural complication		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Post procedural discomfort		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Post procedural swelling		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	2
Procedural pain		
subjects affected / exposed	5 / 10 (50.00%)	3 / 15 (20.00%)
occurrences (all)	6	4
Procedural vomiting		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Radial head dislocation		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Skin abrasion		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	2	1
Skin laceration		

subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Stoma site hypergranulation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Stoma site pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Subdural haematoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urethral injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Venomous sting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Developmental hip dysplasia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Cryptorchism			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Epilepsy congenital subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Hypermobility syndrome subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Micrognathia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	5 / 15 (33.33%) 6	
Angina pectoris subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Nervous system disorders Areflexia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 15 (13.33%) 2	
Generalised tonic-clonic seizure subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Dysarthria subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	7 / 15 (46.67%) 8	
Extensor plantar response subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Facial paresis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Febrile convulsion			

subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	5	0
Clonus		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Gross motor delay		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Headache		
subjects affected / exposed	3 / 10 (30.00%)	3 / 15 (20.00%)
occurrences (all)	5	7
Hyperreflexia		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Hypotonia		
subjects affected / exposed	0 / 10 (0.00%)	4 / 15 (26.67%)
occurrences (all)	0	4
Loss of consciousness		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Migraine		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Motor developmental delay		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Muscle contractions involuntary		
subjects affected / exposed	1 / 10 (10.00%)	8 / 15 (53.33%)
occurrences (all)	1	8
Myoclonus		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Peripheral sensory neuropathy		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Pleocytosis		

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Speech disorder developmental			
subjects affected / exposed	0 / 10 (0.00%)	5 / 15 (33.33%)	
occurrences (all)	0	5	
Speech disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Unresponsive to stimuli			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	8 / 15 (53.33%)	
occurrences (all)	0	8	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Hypochromic anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Anaemia			
subjects affected / exposed	3 / 10 (30.00%)	4 / 15 (26.67%)	
occurrences (all)	4	6	
Lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lymphocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Neutrophilia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Tympanic membrane perforation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Excessive cerumen production			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Motion sickness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hyperacusis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Strabismus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Myopia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypermetropia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Heterophoria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye discharge			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eczema eyelids			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dacryostenosis acquired			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Astigmatism			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Anisocoria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lip swelling			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lip pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Infantile colic		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)
occurrences (all)	3	3
Frequent bowel movements		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Flatulence		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Abdominal pain		
subjects affected / exposed	3 / 10 (30.00%)	0 / 15 (0.00%)
occurrences (all)	4	0
Dyspepsia		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Diarrhoea		
subjects affected / exposed	6 / 10 (60.00%)	4 / 15 (26.67%)
occurrences (all)	11	4
Dental caries		
subjects affected / exposed	2 / 10 (20.00%)	3 / 15 (20.00%)
occurrences (all)	4	3
Constipation		
subjects affected / exposed	1 / 10 (10.00%)	7 / 15 (46.67%)
occurrences (all)	2	9
Breath odour		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Abdominal pain upper		
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Dysphagia		
subjects affected / exposed	0 / 10 (0.00%)	5 / 15 (33.33%)
occurrences (all)	0	5

Vomiting			
subjects affected / exposed	5 / 10 (50.00%)	10 / 15 (66.67%)	
occurrences (all)	15	30	
Toothache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Teething			
subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Salivary hypersecretion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	3	
Malocclusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Dermatitis allergic			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Dermatitis atopic			

subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	2	1
Dermatitis contact		
subjects affected / exposed	3 / 10 (30.00%)	1 / 15 (6.67%)
occurrences (all)	4	1
Dermatitis diaper		
subjects affected / exposed	2 / 10 (20.00%)	3 / 15 (20.00%)
occurrences (all)	2	3
Erythema		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Eczema nummular		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Eczema		
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	10
Hidradenitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Seborrhoeic dermatitis		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Rash pruritic		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Rash papular		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Rash maculo-papular		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Rash erythematous		
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Rash		

subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
Ichthyosis acquired			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Miliaria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Photosensitivity reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin irritation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin hypopigmentation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	3	2	
Superficial inflammatory dermatosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Micturition urgency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Leukocyturia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Bladder hypertrophy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Ligament laxity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Acquired plagiocephaly			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Barrel chest			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Clubbing			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Coccydynia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Foot deformity			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	4	
Growth failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Joint contracture			

subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Joint range of motion decreased		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Kyphosis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Osteopenia		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Pain in extremity		
subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)
occurrences (all)	2	3
Scoliosis		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Synovitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Tendon disorder		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Toe walking		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Neck pain		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Muscle atrophy		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Muscle contracture		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Muscle spasms		

subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Muscle twitching			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 10 (10.00%)	9 / 15 (60.00%)	
occurrences (all)	1	10	
Lordosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Torticollis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Trismus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Winged scapula			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Bacterial labyrinthitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear infection bacterial			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	4	
Ear infection			
subjects affected / exposed	2 / 10 (20.00%)	4 / 15 (26.67%)	
occurrences (all)	4	7	
Dysentery			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Cystitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Croup infectious		
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	3
Covid-19		
subjects affected / exposed	2 / 10 (20.00%)	5 / 15 (33.33%)
occurrences (all)	2	7
Conjunctivitis		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Cellulitis		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Bronchitis viral		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Bronchitis		
subjects affected / exposed	1 / 10 (10.00%)	5 / 15 (33.33%)
occurrences (all)	4	11
Bronchiolitis		
subjects affected / exposed	0 / 10 (0.00%)	4 / 15 (26.67%)
occurrences (all)	0	4
Influenza		
subjects affected / exposed	4 / 10 (40.00%)	6 / 15 (40.00%)
occurrences (all)	9	7
Impetigo		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Hand-foot-and-mouth disease		
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	3
Gingivitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1

Gastrointestinal viral infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Labyrinthitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	2 / 15 (13.33%) 2
Fungal skin infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0
Eye infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 15 (0.00%) 0
Enterovirus infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 15 (6.67%) 1
Ear infection staphylococcal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Gastroenteritis viral subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5	4 / 15 (26.67%) 5
Otitis media acute subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 15 (20.00%) 3
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4	3 / 15 (20.00%) 7
Otitis externa subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1
Oral herpes subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	0 / 15 (0.00%) 0

Oral candidiasis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	7 / 10 (70.00%)	11 / 15 (73.33%)
occurrences (all)	34	34
Metapneumovirus infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Lice infestation		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Laryngitis		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Otitis media bacterial		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)
occurrences (all)	1	2
Pharyngitis streptococcal		
subjects affected / exposed	1 / 10 (10.00%)	5 / 15 (33.33%)
occurrences (all)	2	5
Pneumonia		
subjects affected / exposed	1 / 10 (10.00%)	7 / 15 (46.67%)
occurrences (all)	1	13
Pneumonia aspiration		
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	3
Pneumonia moraxella		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Respiratory syncytial virus infection		
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)
occurrences (all)	1	4

Otitis media		
subjects affected / exposed	5 / 10 (50.00%)	6 / 15 (40.00%)
occurrences (all)	7	10
Stoma site infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Skin infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Sinusitis bacterial		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	4
Sinusitis		
subjects affected / exposed	3 / 10 (30.00%)	4 / 15 (26.67%)
occurrences (all)	3	5
Rotavirus infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Rhinovirus infection		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	3
Rhinitis		
subjects affected / exposed	2 / 10 (20.00%)	3 / 15 (20.00%)
occurrences (all)	4	10
Respiratory tract infection viral		
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Respiratory tract infection bacterial		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Streptococcal infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Tinea pedis		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	2	0

Tinea infection		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Tonsillitis		
subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)
occurrences (all)	4	3
Upper respiratory tract infection		
subjects affected / exposed	7 / 10 (70.00%)	11 / 15 (73.33%)
occurrences (all)	20	49
Vulvovaginal mycotic infection		
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Vulvovaginal candidiasis		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Viral upper respiratory tract infection		
subjects affected / exposed	3 / 10 (30.00%)	6 / 15 (40.00%)
occurrences (all)	7	11
Viral rhinitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Viral rash		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Viral pharyngitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Viral infection		
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	3
Varicella		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Urinary tract infection bacterial		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	4	1

Urinary tract infection subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	4 / 15 (26.67%) 5	
Metabolism and nutrition disorders			
Iron deficiency subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Acidosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Decreased appetite subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	0 / 15 (0.00%) 0	
Dehydration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 15 (20.00%) 3	
Failure to thrive subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Feeding disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Feeding intolerance subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Food intolerance subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Hypophagia			

subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Lipid metabolism disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vitamin d deficiency			
subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Weight gain poor			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Metabolic acidosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2014	- The primary reason was to update the Sponsor Information.
18 December 2014	- The primary reason for this amendment to Protocol 232SM201 is to accommodate the inclusion of twins with spinal muscular atrophy (SMA).
30 September 2015	- The Schedule of Activities (SoA) was updated to include sibling SMA data collection at Screening and Day 868/Early Termination. - A footnote was added to the SoA to indicate that optional videotaping during the CHOP INTEND test will be conducted. - Inclusion criterion 5 was updated to provide additional clarification regarding the location of the CMAP assessment.
15 December 2015	- The interim analysis section was updated to include formal data reviews.
20 March 2017	- The primary reason for this amendment to Protocol 232SM201 is to provide subjects with presymptomatic spinal muscular atrophy (SMA) with the opportunity to receive open-label nusinersen until subjects are 5 years of age (60 months).
02 October 2019	- The scheduled visit period was extended up to 8 years after the first injection of nusinersen. Table 3 was revised to present the schedule of activities from Day 897 through Day 1730. Table 4 was added to present the schedule of activities from Day 1849 through Day 2891 (end of study). - Allowed concomitant therapy was edited, and disallowed concomitant therapy was removed. - The clarification on the use of cognitive scales was provided. - New assessments quality of voice, echocardiograms, and speech and sensory nerve action potential were added. - Clarification on the adverse events was provided.
12 November 2019	- The collection of CSF samples taken predose for pharmacokinetic (PK) and SMN protein analysis and plasma samples for PK analysis was added at Days 1849, 1968, 2206, 2325, 2563, and 2682. In addition, the footnote for plasma samples for PK analysis was updated to specify that plasma will be used to assess phosphorylated neurofilament heavy subunit.
17 October 2021	- The primary reason for this amendment to Protocol 232SM201 is to limit the number of participants who are receiving nusinersen concomitantly with other SMA therapies to 20% (n= 5) of the total population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported