Clinical trial results:
A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Infantile-onset Spinal Muscular Atrophy

Summary

EudraCT number	2013-004422-29
Trial protocol	IT GB ES SE DE BE
Global end of trial date	21 November 2016

Results information

Result version number	v1
This version publication date	01 June 2017
First version publication date	01 June 2017

Trial information

Trial identification

Sponsor protocol code	ISIS 396443-CS3B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02193074
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen 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)	EMEA-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	21 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to examine the clinical efficacy of nusinersen (ISIS 396443) administered intrathecally (IT) to subjects with infantile-onset spinal muscular atrophy (SMA). The secondary objective of the study is to examine the safety and tolerability of nusinersen administered IT to subjects with infantile-onset SMA.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. 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	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Korea, Republic of: 1
Worldwide total number of subjects	122
EEA total number of subjects	47

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	122
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: -

Pre-assignment

Screening details:

After parental informed consent was obtained and prior to any treatment, subjects entered a Screening Period of up to 21 days to determine their eligibility for the study. Of the 149 subjects screened, 27 were screening failures.

Pre-assignment period milestones

Number of subjects started	122
Number of subjects completed	121

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Withdrew prior to receiving treatment: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Sham procedure administered on Study Days 1, 15, 29, 64, 183, and 302.

Arm type	Sham Comparator

No investigational medicinal product assigned in this arm

Arm title	Nusinersen

Arm description:

Nusinersen (2.4 mg/mL) administered as an intrathecal (IT) lumbar puncture injection on Study Days 1, 15, 29, 64, 183, and 302.

Arm type	Experimental
Investigational medicinal product name	nusinersen
Investigational medicinal product code	ISIS 396443
Other name	BIIB058, Spinraza, IONIS-SMN Rx, ISIS SMNRx
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects randomized to the ISIS 396443 treatment group received a single IT LP injection of study treatment as a slow bolus (1 to 3 minutes) using a spinal anesthesia needle and 5-mL syringe on Study Days 1, 15, 29, 64, 183, and 302.

Number of subjects in period 1[1]	Control	Nusinersen
Started	41	80
Completed During Follow-Up Period	11 [2]	26 [3]
Completed Due to Early Study Termination	13 [4]	39 [5]
Completed	24	65
Not completed	17	15
Consent withdrawn by subject	1	2
Adverse event, non-fatal	16	13

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject withdrew prior to receiving treatment and is accounted for in the Pre-Assignment Details.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones describe the subjects' completion status.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones describe the subjects' completion status.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones describe the subjects' completion status.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones describe the subjects' completion status.

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Sham procedure administered on Study Days 1, 15, 29, 64, 183, and 302.	
Reporting group title	Nusinersen
Reporting group description:	
Nusinersen (2.4 mg/mL) administered as an intrathecal (IT) lumbar puncture injection on Study Days 1, 15, 29, 64, 183, and 302.	

Reporting group values	Control	Nusinersen	Total
Number of subjects	41	80	121
Age categorical Units: Subjects			
Age Continuous Units: days			
arithmetic mean	164.7	147.2	
standard deviation	± 48.54	± 46.85	-
Gender, Male/Female Units: Subjects			
Female	24	43	67
Male	17	37	54
Age Continuous | Age at First Dose Units: days			
arithmetic mean	180.5	163.4	
standard deviation	± 50.92	± 49.57	-

End points

End points reporting groups	
Reporting group title	Control
Reporting group description:	
Sham procedure administered on Study Days 1, 15, 29, 64, 183, and 302.	
Reporting group title	Nusinersen
Reporting group description:	
Nusinersen (2.4 mg/mL) administered as an intrathecal (IT) lumbar puncture injection on Study Days 1, 15, 29, 64, 183, and 302.	

Primary: Percentage of Motor Milestones Responders	
End point title	Percentage of Motor Milestones Responders
End point description:	
The definition of a motor milestones responder was based on improvement in the motor milestones categories in Section 2 of the Hammersmith Infant Neurological Examination (HINE), with the exclusion of voluntary grasp, as follows: (i) subject demonstrates ≥ 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking, and (ii) among the motor milestone categories, with the exclusion of voluntary grasp, there are more categories where there is improvement as defined in (i) than worsening. (For the category of ability to kick, worsening is defined as ≥ 2-point decrease or decrease to the lowest possible score of no kicking. For the other categories, worsening is defined as ≥ 1-point decrease.) The lowest possible score for the HINE is 0 (zero), and the highest possible score for the HINE is 28.	
End point type	Primary
End point timeframe:	
assessed at the later of the Day 183, Day 302, or Day 394 study visits	

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	73		
Units: percentage of participants	0	51		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	50.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	31.81
upper limit	66.48

Primary: Time to Death or Permanent Ventilation

End point title	Time to Death or Permanent Ventilation

End point description:

Estimated proportion of participants who died or required permanent ventilation by a given study day, based on the Kaplan-Meier product-limit method. Time to death or permanent ventilation was defined as either tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event. This endpoint was adjudicated by a blinded, independent group of experienced clinicians, the Event Adjudication Committee (EAC), based on review of clinical study data and supporting information. Results are based on all available data.

End point type	Primary

End point timeframe:

Day 91, Day 182, Day 273, Day 364, Day 394

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: proportion of participants				
number (not applicable)				
By Day 91 (13 weeks/3 months)	0.268	0.24		
By Day 182 (26 weeks/6 months)	0.605	0.294		
By Day 273 (39 weeks/9 months)	0.702	0.404		
By Day 364 (52 weeks/12 months)	0.735	0.447		
By Day 394 (13 months)	0.735	0.447		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046
Method	Logrank

Statistical analysis title	Statistical Analysis 2
Comparison groups	Control v Nusinersen

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0164
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3156
upper limit	0.8902

Secondary: Percentage of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) Responders

End point title	Percentage of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) Responders

End point description:

A participant was considered a CHOP-INTEND responder if the change from baseline in CHOP-INTEND total score is ≥ 4 points based on assessment at the later of the Day 183, Day 302, or Day 394 study visits. CHOP-INTEND tests includes 16 items structured to move from easiest to hardest with the grading including gravity eliminated (lower scores) to antigravity movements (higher scores). Total scores range from 0 to 64, with higher scores indicating better movement functioning. Results are based on all available data.

End point type	Secondary

End point timeframe:

assessed at Baseline and the later of the Day 183, Day 302, or Day 394 study visits

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	73		
Units: percentage of participants	3	71		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	DIfference in percentages
Point estimate	68.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	51.27
upper limit	81.99

Secondary: Summary of Time to Death

End point title	Summary of Time to Death

End point description:

Estimated proportion of participants who died by given duration thresholds, based on the Kaplan-Meier product-limit method.

End point type	Secondary

End point timeframe:

Day 91, Day 182, Day 273, Day 364, Day 394

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: proportion of particiants				
number (not applicable)				
by Day 91	0.195	0.101		
by Day 182	0.348	0.141		
by Day 273	0.382	0.173		
by Day 364	0.419	0.173		
by Day 394	0.419	0.173		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082
Method	Cox proportional hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.372
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1787
upper limit	0.7745

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0041
Method	Logrank

Secondary: Percentage of Participants Not Requiring Permanent Ventilation

End point title	Percentage of Participants Not Requiring Permanent Ventilation

End point description:

End point type	Secondary

End point timeframe:

Up to Day 394

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	80		
Units: percentage of participants	68	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Compound Muscular Action Potential (CMAP) Responders

End point title	Percentage of Compound Muscular Action Potential (CMAP) Responders

End point description:

CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles. A participant was defined as a CMAP responder if the CMAP amplitude at the peroneal nerve was increasing to or maintained at ≥ 1 mV (comparing to the baseline) based on assessment at the later of the Day 183, Day 302, or Day 394 study visits. Results are based on all available data.

End point type	Secondary

End point timeframe:

assessed at the later of the Day 183, Day 302, or Day 394 study visits

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	73		
Units: percentage of participants	5	36		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	30.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.35
upper limit	48.09

Secondary: Time to Death or Respiratory Intervention in the Subgroup of Participants Below the Study Median Disease Duration

End point title	Time to Death or Respiratory Intervention in the Subgroup of Participants Below the Study Median Disease Duration

End point description:

Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) among participants below the study median disease duration (13.1 weeks), by given duration thresholds, based on the Kaplan-Meier product-limit method.

End point type	Secondary

End point timeframe:

Day 91, Day 182, Day 273, Day 364, Day 394

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	39		
Units: proportion of participants				
number (not applicable)				
by Day 91	0.238	0.128		
by Day 182	0.546	0.128		
by Day 273	0.697	0.228		
by Day 364	0.773	0.271		
by Day 394	0.773	0.271		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Logrank

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	Cox proportional hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1002
upper limit	0.5753

Secondary: Time to Death or Respiratory Intervention in the Subgroup of Participants Above the Study Median Disease Duration

End point title	Time to Death or Respiratory Intervention in the Subgroup of Participants Above the Study Median Disease Duration

End point description:

Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) among participants above the study median disease duration (13.1 weeks), by given duration thresholds, based on the Kaplan-Meier product-limit method.

End point type	Secondary

End point timeframe:

Day 91, Day 182, Day 273, Day 364, Day 394

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	41		
Units: proportion of participants				
number (not applicable)				
by Day 91	0.3	0.35		
by Day 182	0.67	0.462		
by Day 273	0.725	0.584		
by Day 364	0.725	0.625		
by Day 394	0.725	0.625		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6268
Method	Cox proportional hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.844
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.427
upper limit	1.6698

Statistical analysis title	Statistical Analysis 1
Comparison groups	Control v Nusinersen
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3953
Method	Logrank

Secondary: Number of Participants Experiencing Adverse Events (AEs), Serious AEs (SAEs) and Discontinuations Due to AEs

End point title	Number of Participants Experiencing Adverse Events (AEs), Serious AEs (SAEs) and Discontinuations Due to AEs

End point description:

AE: any unfavorable and unintended sign, symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product. SAE: any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria: results in death; is life threatening: that is, poses an immediate risk of death at the

time of the event; requires in-patient hospitalization or prolongation of existing hospitalization; results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; results in congenital anomaly or birth defect in the offspring of the participant (whether male or female); is an important medical event in the opinion of the Investigator or Sponsor.

End point type	Secondary

End point timeframe:

Screening through Day 394 (± 7 days) or early termination

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	80		
Units: partiicipants				
Any event	40	77		
Moderate or severe event	39	70		
Severe event	33	45		
Possibly related or related event	6	9		
Related event	0	0		
Serious event	39	61		
Related serious event	0	0		
Treatment discontinuation due to an event	16	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AEs Corresponding to Changes in Hematology Values

End point title	Number of Participants With AEs Corresponding to Changes in Hematology Values

End point description:

End point type	Secondary

End point timeframe:

up to Day 394 (± 7 days) or early termination

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	80		
Units: participants				
Anemia	1	1		
Neutrophil count increased	0	1		
Leukocytosis	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AEs Corresponding to Changes in Blood Chemistry Values

End point title	Number of Participants With AEs Corresponding to Changes in Blood Chemistry Values

End point description:

End point type	Secondary

End point timeframe:

up to Day 394 (± 7 days) or early termination

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	80		
Units: participants				
Blood potassium decreased	0	2		
Liver function test abnormal	0	1		
Alanine aminotransferase increased	0	1		
Aspartate aminotransferase increased	0	1		
Blood chloride decreased	0	1		
Blood iron decreased	0	1		
Blood sodium decreased	0	1		
C-reactive protein increased	1	2		
Hypokalemia	3	2		
Hypoglycemia	2	0		
Hyperglycemia	1	0		
Transaminases increased	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Meeting Selected Vital Sign Criteria Post-Baseline

End point title	Number of Participants Meeting Selected Vital Sign Criteria Post-Baseline

End point description:

End point type	Secondary

End point timeframe:

up to Day 394 (± 7 days) or early termination

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[1]	80		
Units: participants				
Systolic blood pressure <90 mmHg	36	74		
Systolic blood pressure >140 mmHg	4	4		
Systolic blood pressure >160 mmHg	0	0		
Diastolic blood pressure <50 mmHg	26	71		
Diastolic blood pressure >90 mmHg	13	12		
Diastolic blood pressure >100 mmHg	3	0		
Pulse rate <60 bpm	0	0		
Pulse rate >100 bpm	41	80		
Temperature >38.0 C	7	6		
Temperature <36.0 C	21	45		
Respiratory rate <12 breaths/min	0	0		
Respiratory rate >20 breaths/min	41	80		
Body weight ≥7% decrease from BL	1	4		
Body weight ≥7% increase from BL	33	67		

Notes:

[1] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Shifts in 12-lead Electrocardiogram (ECG) Results

End point title	Summary of Shifts in 12-lead Electrocardiogram (ECG) Results

End point description:

Shift to ‘abnormal, not clinically significant’ includes ‘unknown’ or ‘normal’ to ‘abnormal, not clinically significant’. Shift to ‘abnormal, clinically significant’ includes ‘unknown’ or ‘normal’ to ‘abnormal, clinically significant’.

End point type	Secondary

End point timeframe:

up to Day 394 (± 7 days) or early termination

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[2]	65[3]		
Units: participants				
Shift to abnormal, not clinically significant	5	17		
Shift to abnormal, clinically significant	0	8		
From unknown to abnormal, clinically significant	0	0		

Notes:

[2] - subjects whose baseline value was not abnormal and who had at least one post-baseline value.

[3] - subjects whose baseline value was not abnormal and who had at least one post-baseline value.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes From Baseline in Urinalysis Values

End point title	Number of Participants With Clinically Significant Changes From Baseline in Urinalysis Values

End point description:

End point type	Secondary

End point timeframe:

up to Day 394 (± 7 days) or early termination

End point values	Control	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	80		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening through Day 394 (± 7 days) or early termination	
Adverse event reporting additional description:	
Treatment-emergent events are presented.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Nusinersen
Reporting group description:	
Nusinersen (2.4 mg/mL) administered as an IT lumbar puncture injection on Study Days 1, 15, 29, 64, 183, and 302.	
Reporting group title	Control
Reporting group description:	
Sham procedure administered on Study Days 1, 15, 29, 64, 183, and 302.	

Serious adverse events	Nusinersen	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 80 (76.25%)	39 / 41 (95.12%)	
number of deaths (all causes)	13	16	
number of deaths resulting from adverse events			
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			
subjects affected / exposed	2 / 80 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			

subjects affected / exposed	1 / 80 (1.25%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respirovirus test positive			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding tube complication			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaccination complication			

subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 80 (2.50%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	5 / 80 (6.25%)	5 / 41 (12.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cyanosis			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical health deterioration			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 80 (5.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical failure			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 80 (2.50%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Retching			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary hypersecretion			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 80 (3.75%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	11 / 80 (13.75%)	9 / 41 (21.95%)	
occurrences causally related to treatment / all	0 / 29	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Apnoea			
subjects affected / exposed	2 / 80 (2.50%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apparent life threatening event			
subjects affected / exposed	0 / 80 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	3 / 80 (3.75%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Atelectasis			
subjects affected / exposed	14 / 80 (17.50%)	4 / 41 (9.76%)	
occurrences causally related to treatment / all	0 / 26	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	1 / 80 (1.25%)	5 / 41 (12.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 80 (5.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoventilation			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	4 / 80 (5.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased bronchial secretion			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	8 / 80 (10.00%)	5 / 41 (12.20%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	5 / 80 (6.25%)	4 / 41 (9.76%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory disorder			
subjects affected / exposed	2 / 80 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	21 / 80 (26.25%)	8 / 41 (19.51%)	
occurrences causally related to treatment / all	0 / 28	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory failure			
subjects affected / exposed	20 / 80 (25.00%)	16 / 41 (39.02%)	
occurrences causally related to treatment / all	0 / 22	0 / 21	
deaths causally related to treatment / all	0 / 4	0 / 8	
Respiratory tract congestion			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	4 / 80 (5.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 80 (5.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	3 / 80 (3.75%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			

subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 80 (5.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Moraxella infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	19 / 80 (23.75%)	5 / 41 (12.20%)	
occurrences causally related to treatment / all	0 / 25	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	3 / 80 (3.75%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia moraxella			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
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	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	6 / 80 (7.50%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (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 bronchiolitis			

subjects affected / exposed	4 / 80 (5.00%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	6 / 80 (7.50%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	7 / 80 (8.75%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site abscess			
subjects affected / exposed	1 / 80 (1.25%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 41 (2.44%)	
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	4 / 80 (5.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 80 (3.75%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	5 / 80 (6.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 80 (3.75%)	6 / 41 (14.63%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 80 (1.25%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder of infancy or early childhood			
subjects affected / exposed	2 / 80 (2.50%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding intolerance			
subjects affected / exposed	2 / 80 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight gain poor			

subjects affected / exposed	3 / 80 (3.75%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nusinersen	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 80 (87.50%)	35 / 41 (85.37%)	
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	9 / 80 (11.25%)	9 / 41 (21.95%)	
occurrences (all)	15	14	
Weight decreased			
subjects affected / exposed	4 / 80 (5.00%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Injury, poisoning and procedural complications			
Feeding tube complication			
subjects affected / exposed	1 / 80 (1.25%)	3 / 41 (7.32%)	
occurrences (all)	1	4	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	4 / 80 (5.00%)	3 / 41 (7.32%)	
occurrences (all)	4	4	
Tachycardia			
subjects affected / exposed	7 / 80 (8.75%)	5 / 41 (12.20%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 80 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Pyrexia			
subjects affected / exposed	43 / 80 (53.75%)	24 / 41 (58.54%)	
occurrences (all)	110	43	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	28 / 80 (35.00%)	9 / 41 (21.95%)	
occurrences (all)	31	9	
Diarrhoea			
subjects affected / exposed	11 / 80 (13.75%)	7 / 41 (17.07%)	
occurrences (all)	14	13	
Dysphagia			
subjects affected / exposed	7 / 80 (8.75%)	9 / 41 (21.95%)	
occurrences (all)	10	11	
Flatulence			
subjects affected / exposed	4 / 80 (5.00%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 80 (12.50%)	8 / 41 (19.51%)	
occurrences (all)	11	8	
Salivary hypersecretion			
subjects affected / exposed	6 / 80 (7.50%)	1 / 41 (2.44%)	
occurrences (all)	6	1	
Teething			
subjects affected / exposed	14 / 80 (17.50%)	3 / 41 (7.32%)	
occurrences (all)	14	3	
Vomiting			
subjects affected / exposed	11 / 80 (13.75%)	7 / 41 (17.07%)	
occurrences (all)	20	7	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	9 / 80 (11.25%)	9 / 41 (21.95%)	
occurrences (all)	19	14	
Bronchial secretion retention			
subjects affected / exposed	4 / 80 (5.00%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
Cough			
subjects affected / exposed	9 / 80 (11.25%)	8 / 41 (19.51%)	
occurrences (all)	11	11	
Dyspnoea			

subjects affected / exposed	3 / 80 (3.75%)	4 / 41 (9.76%)	
occurrences (all)	3	5	
Hypoxia			
subjects affected / exposed	4 / 80 (5.00%)	2 / 41 (4.88%)	
occurrences (all)	5	3	
Nasal congestion			
subjects affected / exposed	8 / 80 (10.00%)	5 / 41 (12.20%)	
occurrences (all)	12	6	
Pneumonia aspiration			
subjects affected / exposed	3 / 80 (3.75%)	3 / 41 (7.32%)	
occurrences (all)	4	3	
Respiratory distress			
subjects affected / exposed	4 / 80 (5.00%)	6 / 41 (14.63%)	
occurrences (all)	4	7	
Respiratory failure			
subjects affected / exposed	0 / 80 (0.00%)	6 / 41 (14.63%)	
occurrences (all)	0	7	
Rhinorrhoea			
subjects affected / exposed	6 / 80 (7.50%)	3 / 41 (7.32%)	
occurrences (all)	7	3	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 80 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Upper respiratory tract congestion			
subjects affected / exposed	6 / 80 (7.50%)	1 / 41 (2.44%)	
occurrences (all)	6	1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 80 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Dermatitis contact			
subjects affected / exposed	2 / 80 (2.50%)	3 / 41 (7.32%)	
occurrences (all)	3	3	
Dermatitis diaper			
subjects affected / exposed	6 / 80 (7.50%)	4 / 41 (9.76%)	
occurrences (all)	6	4	

Erythema			
subjects affected / exposed	1 / 80 (1.25%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Rash			
subjects affected / exposed	9 / 80 (11.25%)	4 / 41 (9.76%)	
occurrences (all)	11	5	
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	4 / 80 (5.00%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
Infections and infestations			
Bacterial tracheitis			
subjects affected / exposed	1 / 80 (1.25%)	4 / 41 (9.76%)	
occurrences (all)	2	9	
Bronchiolitis			
subjects affected / exposed	4 / 80 (5.00%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
Candida infection			
subjects affected / exposed	0 / 80 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	6	
Conjunctivitis			
subjects affected / exposed	5 / 80 (6.25%)	3 / 41 (7.32%)	
occurrences (all)	5	3	
Ear infection			
subjects affected / exposed	5 / 80 (6.25%)	1 / 41 (2.44%)	
occurrences (all)	7	1	
Influenza			
subjects affected / exposed	5 / 80 (6.25%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Nasopharyngitis			
subjects affected / exposed	14 / 80 (17.50%)	4 / 41 (9.76%)	
occurrences (all)	20	4	
Oral candidiasis			
subjects affected / exposed	7 / 80 (8.75%)	3 / 41 (7.32%)	
occurrences (all)	9	4	
Pneumonia			

subjects affected / exposed	7 / 80 (8.75%)	3 / 41 (7.32%)	
occurrences (all)	8	3	
Respiratory tract infection			
subjects affected / exposed	4 / 80 (5.00%)	2 / 41 (4.88%)	
occurrences (all)	10	2	
Rhinitis			
subjects affected / exposed	2 / 80 (2.50%)	3 / 41 (7.32%)	
occurrences (all)	6	4	
Rhinovirus infection			
subjects affected / exposed	4 / 80 (5.00%)	4 / 41 (9.76%)	
occurrences (all)	5	5	
Stoma site infection			
subjects affected / exposed	1 / 80 (1.25%)	3 / 41 (7.32%)	
occurrences (all)	1	4	
Upper respiratory tract infection			
subjects affected / exposed	22 / 80 (27.50%)	9 / 41 (21.95%)	
occurrences (all)	36	12	
Urinary tract infection			
subjects affected / exposed	6 / 80 (7.50%)	0 / 41 (0.00%)	
occurrences (all)	7	0	
Viral infection			
subjects affected / exposed	4 / 80 (5.00%)	3 / 41 (7.32%)	
occurrences (all)	5	3	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 80 (7.50%)	1 / 41 (2.44%)	
occurrences (all)	9	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 80 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2014	- Finalized aspects of the study design.
20 June 2014	- Added language explaining that all primary endpoint events were to be reviewed in a blinded fashion by a central, independent adjudication committee. - Added language to specify the segregation of responsibilities and blinding for personnel making decisions regarding subjects' ventilation and performing efficacy evaluations.
22 April 2016	- Clarification was made to allow subjects who complete all study assessments to rollover into a long-term extension study in the scenario of the study being terminated early based on the assessment of risk-benefit of ISIS 396443 as a result of the interim analysis. - A statement was added related to unblinding of certain representatives from the study Sponsor during the conduct of the interim analysis. - Clarification was made on the adjustment of visit schedule for subjects who experience treatment delays as a result of an illness. - Changes were made to the primary and secondary efficacy endpoints based on new information from Phase 2 and natural history data and to improve ability to interpret some of the endpoints in the event that the study is terminated early. - A sample size justification was added based on the power analysis using the new primary endpoint of motor milestone responders. - Timing of the interim and final analyses was clarified. - Clinical experience was updated to reflect the most recent version of the Investigator's Brochure. - A definition for Interim Efficacy Set was added. - A description of the endpoints and timing of the interim analysis was added. - Details on the definitions of primary, secondary, and tertiary endpoints were added. - References related to analytical methods were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported