



## Clinical trial results:

### A Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Nusinersen (ISIS 396443) Delivered Intrathecally to Patients with Infantile-Onset Spinal Muscular Atrophy

#### Summary

EudraCT number	2017-000621-12
Trial protocol	Outside EU/EEA
Global end of trial date	21 August 2017

#### Results information

Result version number	v1
This version publication date	03 March 2018
First version publication date	03 March 2018

#### Trial information

##### Trial identification

Sponsor protocol code	ISIS 396443-CS3A
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01839656
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 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	21 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 August 2017
Global end of trial reached?	Yes
Global end of trial date	21 August 2017
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to examine the clinical efficacy of multiple doses of Nusinersen (ISIS 396443) when administered intrathecally to subjects with infantile-onset 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	08 May 2013
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: 18
Country: Number of subjects enrolled	Canada: 3
Worldwide total number of subjects	21
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	21
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:

Of the 23 subjects screened, 2 were screening failures. A total of 21 subjects enrolled; 1 was withdrawn from the study prior to receiving the first dose of study treatment. Twenty subjects received at least 1 dose of study treatment and were included in the efficacy, safety, and PK analyses.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nusinersen 6 mg

Arm description:

Subjects received nusinersen 6 mg injections as an intrathecal (IT) bolus through a lumbar puncture (LP) on Days 1, 15, and 85. Maintenance doses of 12 mg were given on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.

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

Dosage and administration details:

Administered as specified in the treatment arm.

<b>Arm title</b>	Nusinersen 12 mg
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Arm description:

Subjects received nusinersen 12 mg injections as an intrathecal (IT) bolus through a lumbar puncture (LP) on Days 1, 15, and 85. Maintenance doses of 12 mg were given on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.

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

Dosage and administration details:

Administered as specified in the treatment arm.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Nusinersen 6 mg	Nusinersen 12 mg
Started	4	16
Completed Loading Dose Period	4	15
Completed	2	0
Not completed	2	16
Adverse event, serious fatal	1	4
Consent withdrawn by subject	1	1
Early study closure	-	11

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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: Of the 21 subjects enrolled, 1 (in Cohort 1) was withdrawn from the study prior to receiving the first dose of study treatment.

## Baseline characteristics

### Reporting groups

Reporting group title	Nusinersen 6 mg
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Reporting group description:

Subjects received nusinersen 6 mg injections as an intrathecal (IT) bolus through a lumbar puncture (LP) on Days 1, 15, and 85. Maintenance doses of 12 mg were given on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.

Reporting group title	Nusinersen 12 mg
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Reporting group description:

Subjects received nusinersen 12 mg injections as an intrathecal (IT) bolus through a lumbar puncture (LP) on Days 1, 15, and 85. Maintenance doses of 12 mg were given on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.

Reporting group values	Nusinersen 6 mg	Nusinersen 12 mg	Total
Number of subjects	4	16	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	4	16	20
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: days			
arithmetic mean	145	140	-
standard deviation	± 67	± 60	
Gender categorical Units: Subjects			
Female	1	7	8
Male	3	9	12
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	4	15	19
Race Units: Subjects			
White	3	13	16
Black	0	1	1
Asian	0	1	1
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple Race	1	0	1
Other	0	1	1

Hammersmith Infant Neurological Examination (HINE) Head Control Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
Unable to maintain head upright	3	13	16
Wobbles	1	2	3
All the time maintained upright	0	1	1
HINE Sitting Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
Cannot sit	4	15	19
Sits with support at hips	0	1	1
Props	0	0	0
Stable sit	0	0	0
Pivots (rotates)	0	0	0
HINE Voluntary Grasp Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
No grasp	0	3	3
Uses whole hand	4	13	17
Index finger and thumb but immature grasp	0	0	0
Pincer grasp	0	0	0
HINE Ability to Kick Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
No kicking	1	5	6
Kick horizontally, legs do not lift	3	10	13
Upward (vertically)	0	1	1
Touches leg	0	0	0
Touches toes	0	0	0
HINE Rolling Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
No rolling	4	15	19
Rolling to side	0	0	0
Prone to supine	0	1	1
Supine to prone	0	0	0
HINE Crawling Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
Does not lift head	4	14	18
On elbow	0	1	1
On outstretched hand	0	1	1
Crawling flat on abdomen	0	0	0
Crawling on hands and knees	0	0	0
HINE Standing Motor Milestones at Baseline			

Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
Does not support weight	4	15	19
Supports weight	0	1	1
Stands with support	0	0	0
Stands unaided	0	0	0
HINE Walking Motor Milestones at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
No walking	4	15	19
Bouncing	0	1	1
Cruising (walks holding on)	0	0	0
Walking independently	0	0	0
Distribution of Total Scores of the CHOP INTEND Motor Function Scale at Baseline			
CHOP INTEND is the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease. Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: Subjects			
0 to 9	0	0	0
10 to 19	0	2	2
20 to 29	3	6	9
30 to 39	1	6	7
40 to 49	0	1	1
50 to 59	0	0	0
60 to 64	0	1	1
Mean CHOP INTEND Total Scores at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: units on a scale			
arithmetic mean	27	30	
standard deviation	± 5	± 12	-
Mean Compound Muscle Action Potential (CMAP) Amplitude of the Peroneal Nerve at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: millivolts (mV)			
arithmetic mean	0.673	0.518	
standard deviation	± 0.501	± 0.664	-
Mean CMAP Amplitude of the Ulnar Nerve at Baseline			
Baseline was defined as the last non-missing value prior to the first dose of nusinersen.			
Units: mV			
arithmetic mean	0.372	0.532	
standard deviation	± 0.177	± 0.878	-



## End points

### End points reporting groups

Reporting group title	Nusinersen 6 mg
Reporting group description: Subjects received nusinersen 6 mg injections as an intrathecal (IT) bolus through a lumbar puncture (LP) on Days 1, 15, and 85. Maintenance doses of 12 mg were given on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.	
Reporting group title	Nusinersen 12 mg
Reporting group description: Subjects received nusinersen 12 mg injections as an intrathecal (IT) bolus through a lumbar puncture (LP) on Days 1, 15, and 85. Maintenance doses of 12 mg were given on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.	

### Primary: Percent of Subjects Who Achieved Improvement in Motor Milestones as Assessed by Section 2 of the HINE at the Last Visit

End point title	Percent of Subjects Who Achieved Improvement in Motor Milestones as Assessed by Section 2 of the HINE at the Last Visit <sup>[1]</sup>
End point description: Section 2 of HINE consists of 8 independent milestone categories. Within each of these categories, subjects can progress from complete absence of a motor ability (the lowest level in each category) through multiple milestones (2 to 4 levels in each category) to the highest level within the category. Overall, there are a total of 26 milestones that can be achieved across the 8 categories. Improvement was defined as any of the following: 1. An increase from baseline of 2 milestones or more, or the achievement of pincer grasp in the voluntary grasp category 2. An increase from baseline of 2 milestones or more, or achievement of touching toes in the ability to kick category 3. An increase from baseline of 1 milestone or more in any of the remaining 6 categories: head control, rolling, sitting, crawling, standing, or walking.	
End point type	Primary
End point timeframe: Baseline, Day 1352 or Early Termination	

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: Statistical analysis was not conducted for this endpoint because there was no comparator in this study.

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[2]</sup>	16 <sup>[3]</sup>		
Units: percent of subjects				
number (not applicable)	25.0	68.8		

Notes:

[2] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

[3] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Event-free Survival at the End of Study

End point title	Event-free Survival at the End of Study
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End point description:

Event-free survival was defined as the percent of subjects who were alive and did not require permanent ventilatory support (defined as tracheostomy or the need for  $\geq 16$  hours ventilation/day continuously for at least 2 weeks in the absence of an acute reversible illness) Event-free survival was estimated using Kaplan-Meier methodology.

End point type	Secondary
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End point timeframe:

Up to Day 1638

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[4]</sup>	16 <sup>[5]</sup>		
Units: percent of subjects				
number (not applicable)	25.0	62.5		

Notes:

[4] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

[5] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent of Subjects With Improved Motor Function at the Last Visit as Assessed by the CHOP-INTEND Motor Function Scale

End point title	Percent of Subjects With Improved Motor Function at the Last Visit as Assessed by the CHOP-INTEND Motor Function Scale
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End point description:

The CHOP-INTEND test includes 16 items structured to move from easiest to hardest with the grading including gravity eliminated (lower scores) to antigravity movements (higher scores). All item scores range from 0 (worst) to 4 (best). Total scores range from 0 to 64, with higher scores indicating better movement functioning. Improvement was defined as an increase in total CHOP INTEND score  $\geq 4$  points from baseline as of the last study visit.

End point type	Secondary
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End point timeframe:

Baseline, Day 1352 or Early Termination

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[6]</sup>	16 <sup>[7]</sup>		
Units: percent of subjects				
number (not applicable)	25.0	62.5		

Notes:

[6] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

[7] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Improvement in Neuromuscular Electrophysiology at the Last Visit as Assessed by the Change From Baseline in CMAP Amplitude

End point title	Improvement in Neuromuscular Electrophysiology at the Last Visit as Assessed by the Change From Baseline in CMAP Amplitude
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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 positive change from Baseline indicates that the number of motor neurons increased.

End point type	Secondary
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End point timeframe:

Baseline, Day 1072

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2 <sup>[8]</sup>	8 <sup>[9]</sup>		
Units: mV				
arithmetic mean (standard deviation)				
Peroneal nerve	1.88 (± 2.58)	2.81 (± 1.28)		
Ulnar nerve	0.776 (± 1.448)	0.685 (± 0.415)		

Notes:

[8] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

[9] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Experiencing Adverse Events (AEs) and/or Serious Adverse Events (SAEs)

End point title	Number of Subjects Experiencing Adverse Events (AEs) and/or Serious Adverse Events (SAEs)
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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 subject (whether male or female); is an important medical event in the opinion of the Investigator or Sponsor.

End point type	Secondary
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End point timeframe:

Up to Day 1352

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[10]</sup>	16 <sup>[11]</sup>		
Units: Number of Subjects				
Any AE	4	16		
Any SAE	3	13		

Notes:

[10] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

[11] - Safety Population: All subjects who were registered and received at least 1 dose of nusinersen.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic (PK) Parameters of Nusinersen in CSF: Maximum Observed Drug Concentration (Cmax)

End point title	Pharmacokinetic (PK) Parameters of Nusinersen in CSF: Maximum Observed Drug Concentration (Cmax)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[12]</sup>	0 <sup>[13]</sup>		
Units: nanograms/milliliter (ng/ml)				
arithmetic mean (standard deviation)	()	()		

Notes:

[12] - Due to the limited CSF samples collected, no CSF PK parameters were calculated.

[13] - Due to the limited CSF samples collected, no CSF PK parameters were calculated.

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK Parameters of Nusinersen in Plasma: Cmax

End point title	PK Parameters of Nusinersen in Plasma: Cmax
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[14]</sup>	16 <sup>[15]</sup>		
Units: ng/ml				
arithmetic mean (standard deviation)	396 (± 311)	829 (± 625)		

Notes:

[14] - PK Population: All subjects who were registered and had at least 1 evaluable postdose PK sample.

[15] - PK Population: All subjects who were registered and had at least 1 evaluable postdose PK sample.

## Statistical analyses

No statistical analyses for this end point

### Secondary: PK Parameters of Nusinersen in Plasma: Time to Reach Cmax (Tmax)

End point title	PK Parameters of Nusinersen in Plasma: Time to Reach Cmax (Tmax)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[16]</sup>	16 <sup>[17]</sup>		
Units: hr				
arithmetic mean (standard deviation)	2.09 (± 1.35)	2.37 (± 1.25)		

Notes:

[16] - PK Population: All subjects who were registered and had at least 1 evaluable postdose PK sample.

[17] - PK Population: All subjects who were registered and had at least 1 evaluable postdose PK sample.

## Statistical analyses

No statistical analyses for this end point

### Secondary: PK Parameters of Nusinersen in Plasma: Area Under the Plasma Concentrations Time Curve From the Time of the IT Dose to Four Hours After Dosing (AUC0-4)

End point title	PK Parameters of Nusinersen in Plasma: Area Under the Plasma Concentrations Time Curve From the Time of the IT Dose to Four Hours After Dosing (AUC0-4)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

<b>End point values</b>	Nusinersen 6 mg	Nusinersen 12 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[18]</sup>	16 <sup>[19]</sup>		
Units: ng x hr/ml				
arithmetic mean (standard deviation)	894 (± 610)	2181 (± 1488)		

Notes:

[18] - PK Population: All subjects who were registered and had at least 1 evaluable postdose PK sample.

[19] - PK Population: All subjects who were registered and had at least 1 evaluable postdose PK sample.

### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Day 1359

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	Cohort 1
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Reporting group description: -

Reporting group title	Cohort 2
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Reporting group description: -

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	13 / 16 (81.25%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	1	4	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumopericardium			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
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	2 / 4 (50.00%)	4 / 16 (25.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			



subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (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	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	2 / 4 (50.00%)	6 / 16 (37.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	5 / 16 (31.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Musculoskeletal and connective tissue disorders			
Synovitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Metapneumovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (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	0 / 4 (0.00%)	5 / 16 (31.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia adenoviral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
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	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonas aeruginosa			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	4 / 16 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
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	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	16 / 16 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Haemangioma			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Capillary fragility			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Essential hypertension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Subgaleal haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Device leakage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Device occlusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	3	
Discomfort			

subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Infusion site extravasation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Injection site bruising			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	2 / 4 (50.00%)	3 / 16 (18.75%)	
occurrences (all)	3	3	
Pain			
subjects affected / exposed	0 / 4 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	3 / 4 (75.00%)	14 / 16 (87.50%)	
occurrences (all)	6	46	
Vessel puncture site bruise			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	3 / 16 (18.75%) 3	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 16 (0.00%) 0	
Apnoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 16 (12.50%) 2	
Apnoeic attack subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Aspiration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Atelectasis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 16 (31.25%) 8	
Bronchial secretion retention subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	2 / 16 (12.50%) 3	
Choking subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Chronic respiratory failure subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	3 / 16 (18.75%) 3	
Cough subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	5 / 16 (31.25%) 11	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 16 (6.25%) 1	
Epistaxis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Hypoxia		
subjects affected / exposed	0 / 4 (0.00%)	4 / 16 (25.00%)
occurrences (all)	0	7
Increased bronchial secretion		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Increased upper airway secretion		
subjects affected / exposed	0 / 4 (0.00%)	5 / 16 (31.25%)
occurrences (all)	0	7
Laryngeal granuloma		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Nasal congestion		
subjects affected / exposed	1 / 4 (25.00%)	6 / 16 (37.50%)
occurrences (all)	3	8
Nasal discharge discolouration		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Pneumonia aspiration		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Pneumothorax		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	3
Pulmonary congestion		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Pulmonary oedema		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Respiratory arrest		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Respiratory distress		



subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	4
Respiratory failure		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Restrictive pulmonary disease		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Rhinitis allergic		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Rhinorrhoea		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Rhonchi		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Sinus congestion		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	2
Sleep apnoea syndrome		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Tachypnoea		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Tracheal disorder		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Upper respiratory tract congestion		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Use of accessory respiratory muscles		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Wheezing		

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 16 (12.50%) 2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 16 (18.75%) 3	
Expressive language disorder			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Investigations			
Bacterial test positive			
subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 16 (0.00%) 0	
Bone density decreased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 16 (12.50%) 2	
Breath sounds abnormal			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Heart rate decreased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Heart rate increased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 3	
Human rhinovirus test positive			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 16 (18.75%) 3	
Moraxella test positive			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
Neutrophil count increased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 16 (12.50%) 3	
Neutrophil percentage increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	3	
Pseudomonas test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Serratia test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Staphylococcus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Streptococcus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)	
occurrences (all)	3	4	
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Ear abrasion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Excoriation			

subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)
occurrences (all)	1	3
Feeding tube complication		
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	5
Joint dislocation		
subjects affected / exposed	1 / 4 (25.00%)	3 / 16 (18.75%)
occurrences (all)	2	3
Laceration		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	3
Lip injury		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Pneumothorax traumatic		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Post gastric surgery syndrome		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Procedural pain		
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	1
Procedural site reaction		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Soft tissue injury		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Sunburn		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Thermal burn		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Tooth injury		

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Urinary retention postoperative			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Clinodactyly			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cryptorchism			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
High arched palate			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hip dysplasia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pectus carinatum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Plagiocephaly			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Cardiomyopathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)	
occurrences (all)	1	3	
Ventricular tachycardia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Drooling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hyporeflexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Muscle contractions involuntary			
subjects affected / exposed	1 / 4 (25.00%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Nystagmus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Speech disorder developmental			
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Eosinophilia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Thrombocytosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Middle ear effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye disorders			
Astigmatism			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Erythema of eyelid			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Eye irritation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eyelid ptosis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Chapped lips			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	8 / 16 (50.00%)	
occurrences (all)	1	9	
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	4 / 16 (25.00%)	
occurrences (all)	3	15	
Flatulence			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Frequent bowel movements			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	6 / 16 (37.50%)	
occurrences (all)	0	6	



Haematemesis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Teething			
subjects affected / exposed	2 / 4 (50.00%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Tongue atrophy			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Tooth crowding			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Traumatic tooth displacement			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	5 / 16 (31.25%)	
occurrences (all)	3	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Blister			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Dermatitis contact			

subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Dermatitis diaper		
subjects affected / exposed	2 / 4 (50.00%)	3 / 16 (18.75%)
occurrences (all)	3	3
Ecchymosis		
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)
occurrences (all)	1	2
Eczema		
subjects affected / exposed	1 / 4 (25.00%)	3 / 16 (18.75%)
occurrences (all)	1	3
Erythema		
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	1
Excessive granulation tissue		
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	3
Heat rash		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Petechiae		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Pruritus		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Rash		
subjects affected / exposed	1 / 4 (25.00%)	5 / 16 (31.25%)
occurrences (all)	3	8
Rash follicular		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Rash papular		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Rosacea		

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin depigmentation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin irritation			
subjects affected / exposed	1 / 4 (25.00%)	3 / 16 (18.75%)	
occurrences (all)	2	3	
Skin ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Subcutaneous emphysema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Deformity thorax			
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Hand deformity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Joint contracture			
subjects affected / exposed	3 / 4 (75.00%)	7 / 16 (43.75%)	
occurrences (all)	11	15	
Joint range of motion decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Joint stiffness			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Kyphoscoliosis		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Kyphosis		
subjects affected / exposed	2 / 4 (50.00%)	3 / 16 (18.75%)
occurrences (all)	3	4
Lordosis		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Osteopenia		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Pain in extremity		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	3
Rib deformity		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Scoliosis		
subjects affected / exposed	2 / 4 (50.00%)	6 / 16 (37.50%)
occurrences (all)	3	8
Spinal deformity		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Synovitis		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Torticollis		
subjects affected / exposed	2 / 4 (50.00%)	2 / 16 (12.50%)
occurrences (all)	2	2
Trismus		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Infections and infestations		

Adenoviral upper respiratory infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Adenovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Bacterial disease carrier			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Bacterial infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Bacterial tracheitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	4	
Bronchiolitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Candida nappy rash			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	4	
Enterovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Erythema infectiosum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fungal skin infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastritis viral			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Gastroenteritis viral		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Gastroenteritis		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Hand-foot-and-mouth disease		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Haemophilus infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Hordeolum		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Moraxella infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Mucocutaneous candidiasis		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	1 / 4 (25.00%)	7 / 16 (43.75%)
occurrences (all)	1	14
Oral candidiasis		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Otitis media		

subjects affected / exposed	1 / 4 (25.00%)	6 / 16 (37.50%)
occurrences (all)	1	8
Parainfluenzae virus infection		
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	1
Pharyngitis streptococcal		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	1 / 4 (25.00%)	5 / 16 (31.25%)
occurrences (all)	2	10
Pneumonia moraxella		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Pneumonia pseudomonas aeruginosa		
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	1
Pneumonia streptococcal		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Pneumonia viral		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Pseudomonas infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Respiratory syncytial virus bronchiolitis		
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	1
Respiratory syncytial virus infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	3 / 4 (75.00%)	4 / 16 (25.00%)
occurrences (all)	18	11

Respiratory tract infection bacterial subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rhinitis subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	3	
Rhinovirus infection subjects affected / exposed	0 / 4 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	5	
Staphylococcal bacteraemia subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Staphylococcal infection subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tracheitis subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	4	
Upper respiratory tract infection subjects affected / exposed	1 / 4 (25.00%)	10 / 16 (62.50%)	
occurrences (all)	2	44	
Urinary tract infection subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Viral infection subjects affected / exposed	0 / 4 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	5	
Viral rash subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders Dehydration			



subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Failure to thrive		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Hyperglycaemia		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Hyperkalaemia		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Hyponatraemia		
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	2
Hypophagia		
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)
occurrences (all)	1	1
Malnutrition		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	1	0
Metabolic alkalosis		
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	1
Weight gain poor		
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)
occurrences (all)	2	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2013	14 August 2013 Changes to the protocol are summarized below: * Changed the dose from 9 mg to 12 mg ISIS 396443 (no participants were dosed at the 9-mg level) * Added additional participants to the study where Cohort 2 could enroll between 4 to approximately 16 participants * Added age at death and age at death or $\geq 16$ hours ventilation/day for $>2$ weeks to the exploratory endpoints * Updated the clinical experience section for the ISIS 396443 CS2 and ISIS 396443 CS12 studies
18 January 2014	18 January 2014 Changes to the protocol are summarized below: * Added 1 additional "maintenance" dose of 12 mg equivalent ISIS 396443 on Study Day 253, approximately 6 months after the participants received their Study Day 85 dose (for all participants – both dose cohorts)
14 March 2014	14 March 2014 Changes to the protocol are summarized below: * Added permanent ventilation, defined as $\geq 16$ hours ventilation/day continuously for $>2$ weeks in the absence of an acute reversible illness, to the combined efficacy endpoint
19 May 2014	19 May 2014 Changes to the protocol are summarized below: * Added 4 additional doses of 12 mg equivalent of ISIS 396443 given once every 4 months to extend the maintenance dosing (i.e., on Days 379, 505, 631, and 757) * Updated the rationale for loading and maintenance dose and regimen * Added study drug injection volume in participants $>24$ months of age * Updated information on preclinical experience
29 May 2015	29 May 2015 Changes to the protocol are summarized below: * Added 4 additional doses of 12 mg equivalent of ISIS 396443 given once every 4 months to extend maintenance dosing (i.e., on Days 883, 1009, 1135, and 1261) * Added the Hammersmith Functional Motor Scale-Expanded as an outcomes measure for all participants who maintain a CHOP-INTEND total score of $\geq 50$ for 2 consecutive study visits * Added a ready-to-use vial configuration of the study treatment * Added language on the possibility to perform an interim analysis to support potential discussions with regulatory agencies
25 January 2016	25 January 2016 Changes to the study protocol are summarized below: * Added "Efficacy" and "Nusinersen" to the study title * Amended Study Objectives to reflect efficacy assessment as the primary study objective and safety and tolerability as secondary study objectives

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Care should be used when interpreting the C<sub>max</sub> and AUC values due to the limited sampling.

Notes: