



Clinical trial results:

An Open-Label, Dose Escalation Study to Assess the Safety, Tolerability and Dose-Range Finding of Multiple Doses of ISIS 396443 Delivered Intrathecally to Patients with Spinal Muscular Atrophy

Summary

EudraCT number	2017-000327-27
Trial protocol	Outside EU/EEA
Global end of trial date	15 January 2015

Results information

Result version number	v1 (current)
This version publication date	24 May 2017
First version publication date	24 May 2017

Trial information

Trial identification

Sponsor protocol code	ISIS 396443 - CS2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01703988
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen, Biogen, clinicaltrials@biogen.com
Scientific contact	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	15 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2015
Global end of trial reached?	Yes
Global end of trial date	15 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will test the safety, tolerability, and pharmacokinetics of escalating doses of nusinersen (ISIS 396443) administered into the spinal fluid either two or three times over the duration of the trial, in participants with spinal muscular atrophy (SMA).

Four dose levels will be evaluated sequentially. Each dose level will be studied in a cohort of approximately 8 participants, where all participants will receive active drug.

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 October 2012
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: 34
Worldwide total number of subjects	34
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)	0
Children (2-11 years)	25

Adolescents (12-17 years)	9
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:

Subjects underwent screening evaluations within 28 days prior to study drug administration.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nusinersen 3 mg

Arm description:

3 mg nusinersen on Days 1, 29, 85, intrathecal (IT) injection

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

Dosage and administration details:

Each subject received multiple IT bolus (1 to 3 minutes) injections of 5 mL of the study drug using a "spinal anesthesia" needle and 5-mL syringe.

Arm title	Nusinersen 6 mg
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Arm description:

6 mg nusinersen on Days 1, 29, 85, IT injection

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

Dosage and administration details:

Each subject received multiple IT bolus (1 to 3 minutes) injections of 5 mL of the study drug using a "spinal anesthesia" needle and 5-mL syringe.

Arm title	Nusinersen 9 mg
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Arm description:

9 mg nusinersen on Days 1 and 85, IT injection

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

Dosage and administration details:

Each subject received multiple IT bolus (1 to 3 minutes) injections of 5 mL of the study drug using a

“spinal anesthesia” needle and 5-mL syringe.

Arm title	Nusinersen 12 mg
Arm description: 12 mg nusinersen on Days 1, 29, 85, IT injection	
Arm type	Experimental
Investigational medicinal product name	nusinersen
Investigational medicinal product code	ISIS 396443
Other name	Spinraza; BIIB058; IONIS SMN Rx; ISIS SMNRx
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Each subject received multiple IT bolus (1 to 3 minutes) injections of 5 mL of the study drug using a “spinal anesthesia” needle and 5-mL syringe.

Number of subjects in period 1	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg
Started	8	8	9
Completed	8	8	9
Not completed	0	0	0
Investigator Judgment	-	-	-

Number of subjects in period 1	Nusinersen 12 mg
Started	9
Completed	8
Not completed	1
Investigator Judgment	1

Baseline characteristics

Reporting groups

Reporting group title	Nusinersen 3 mg
Reporting group description:	
3 mg nusinersen on Days 1, 29, 85, intrathecal (IT) injection	
Reporting group title	Nusinersen 6 mg
Reporting group description:	
6 mg nusinersen on Days 1, 29, 85, IT injection	
Reporting group title	Nusinersen 9 mg
Reporting group description:	
9 mg nusinersen on Days 1 and 85, IT injection	
Reporting group title	Nusinersen 12 mg
Reporting group description:	
12 mg nusinersen on Days 1, 29, 85, IT injection	

Reporting group values	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg
Number of subjects	8	8	9
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)	0	0	0
Children (2-11 years)	5	5	8
Adolescents (12-17 years)	3	3	1
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	8.6	8.1	6
standard deviation	± 5.4	± 5.2	± 4
Gender, Male/Female Units: Participants			
Female	4	3	4
Male	4	5	5

Reporting group values	Nusinersen 12 mg	Total	
Number of subjects	9	34	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	7	25	
Adolescents (12-17 years)	2	9	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	6.9		
standard deviation	± 4.3	-	
Gender, Male/Female			
Units: Participants			
Female	3	14	
Male	6	20	

End points

End points reporting groups

Reporting group title	Nusinersen 3 mg
Reporting group description: 3 mg nusinersen on Days 1, 29, 85, intrathecal (IT) injection	
Reporting group title	Nusinersen 6 mg
Reporting group description: 6 mg nusinersen on Days 1, 29, 85, IT injection	
Reporting group title	Nusinersen 9 mg
Reporting group description: 9 mg nusinersen on Days 1 and 85, IT injection	
Reporting group title	Nusinersen 12 mg
Reporting group description: 12 mg nusinersen on Days 1, 29, 85, IT injection	

Primary: Number of Participants With Adverse Events (AEs), Serious AEs (SAEs), Discontinuations Due to AEs, and Highest Severity of AEs

End point title	Number of Participants With Adverse Events (AEs), Serious AEs (SAEs), Discontinuations Due to AEs, and Highest Severity of AEs ^[1]
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End point description:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the study or use of the investigational drug product, whether or not the AE is considered related to the investigational drug product. An SAE is any AE that, in the view of either the Investigator or Sponsor, meets any of the following criteria: results in death; is life threatening; requires inpatient 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; and is an important medical event in the judgment of the investigator. Drug-related is an event related or possibly related to study drug. Severity of AEs was assessed as mild, moderate, or severe.

End point type	Primary
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End point timeframe:

Participants were followed for the duration of the study; mean (SD) duration of treatment was 82.9 (15.4) days

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: Descriptive statistics are presented, per protocol.

End point values	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg	Nusinersen 12 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9	9
Units: Participants				
number (not applicable)				
Any AE	8	6	9	9
Any drug-related AE	0	0	0	0
Any SAE	2	0	0	1
Discontinued due to an AE	0	0	0	0
Highest severity of AE=mild	2	2	6	5
Highest severity of AE=moderate	4	2	3	4
Highest severity of AE=severe	2	2	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics: Maximal Observed Plasma Drug Concentration (C_{max})

End point title	Plasma Pharmacokinetics: Maximal Observed Plasma Drug Concentration (C _{max})
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 and Day 85

End point values	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg	Nusinersen 12 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9	9
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	51.5 (± 72.7)	79.8 (± 57.2)	141 (± 52.8)	208 (± 110)
Day 85	32.5 (± 32.3)	52.8 (± 33.5)	127 (± 37.7)	132 (± 85.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics: Time to Reach C_{max} in Plasma

End point title	Plasma Pharmacokinetics: Time to Reach C _{max} in Plasma
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 and Day 85

End point values	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg	Nusinersen 12 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9	9
Units: hours				
median (full range (min-max))				
Day 1	5.09 (2.03 to 12)	5.93 (2 to 23)	3.92 (2 to 8.03)	4.05 (1.97 to 12)
Day 85	6.08 (4.12 to 6.17)	6.04 (5.97 to 6.25)	4.12 (2 to 6.25)	5.92 (1.95 to 6.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics: Plasma Pharmacokinetics: Area Under the Plasma Concentration Time Curve From the Time of the IT Dose to 6 Hours After Dosing (AUC0-6hr)

End point title	Plasma Pharmacokinetics: Plasma Pharmacokinetics: Area Under the Plasma Concentration Time Curve From the Time of the IT Dose to 6 Hours After Dosing (AUC0-6hr)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 and Day 85

End point values	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg	Nusinersen 12 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9	9
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Day 1	181 (± 225)	306 (± 259)	601 (± 249)	823 (± 442)
Day 85	110 (± 107)	179 (± 135)	524 (± 185)	555 (± 398)

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal Fluid (CSF) Pharmacokinetics: Predose CSF Drug Concentrations

End point title	Cerebrospinal Fluid (CSF) Pharmacokinetics: Predose CSF Drug Concentrations
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End point description:

End point type	Secondary
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End point timeframe:

Day 1, Day 29, and Day 85

End point values	Nusinersen 3 mg	Nusinersen 6 mg	Nusinersen 9 mg	Nusinersen 12 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9 ^[2]	9 ^[3]
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	0.0651 (± 0.117)	0.056 (± 0.104)	99999 (± 99999)	99999 (± 99999)
Day 29	1.41 (± 0.456)	2.65 (± 1.44)	999999 (± 999999)	2.22 (± 0.924)
Day 85	2.12 (± 0.573)	3.76 (± 2.05)	1.5 (± 0.447)	3.36 (± 1.04)

Notes:

[2] - 99999=below the limit of quantification (50 pg/mL). 999999=not applicable since 0 subjects analyzed.

[3] - 99999=below the limit of quantification (50 pg/mL).

Statistical analyses

No statistical analyses for this end point

Secondary: Urine Pharmacokinetics: Renal Clearance, Cohort 4

End point title	Urine Pharmacokinetics: Renal Clearance, Cohort 4 ^[4]
End point description: Renal clearance of nusinersen for participants was assessed in the 12 mg reporting group only, per protocol.	
End point type	Secondary
End point timeframe: Day 1 and Day 85	

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Cohort 4 only are presented for this endpoint, per protocol.

End point values	Nusinersen 12 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mL/hr				
arithmetic mean (standard deviation)				
Day 1	0.674 (± 0.602)			
Day 85	77.5 (± 92.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were followed for the duration of the study; mean (SD) duration of treatment was 82.9 (15.4) days.

Adverse event reporting additional description:

Treatment emergent AEs are presented regardless of seriousness or relationship to investigational product.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	Nusinersen 3 mg
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Reporting group description:

3 mg nusinersen on Days 1, 29, 85, IT injection

Reporting group title	Nusinersen 9 mg
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Reporting group description:

9 mg nusinersen on Days 1 and 85, IT injection

Reporting group title	Nusinersen 12 mg
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Reporting group description:

12 mg nusinersen on Days 1, 29, 85, IT injection

Reporting group title	Nusinersen 6 mg
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Reporting group description:

6 mg nusinersen on Days 1, 29, 85, IT injection

Serious adverse events	Nusinersen 3 mg	Nusinersen 9 mg	Nusinersen 12 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome	Additional description: Event considered not related to study drug, and related to lumbar puncture.		
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity	Additional description: Event assessed as unlikely to be related to study drug.		

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Nusinersen 6 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
	Additional description: Event considered not related to study drug, and related to lumbar puncture.		
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
	Additional description: Event assessed as unlikely to be related to study drug.		
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Nusinersen 3 mg	Nusinersen 9 mg	Nusinersen 12 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	9 / 9 (100.00%)	9 / 9 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
Puncture site pain			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	2 / 9 (22.22%)
occurrences (all)	0	4	2
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	3 / 9 (33.33%)
occurrences (all)	0	0	3
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Catheter site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Catheter site related reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gravitational oedema			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	1
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Atelectasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nasal congestion			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Restrictive pulmonary disease subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Dysphoria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Parasomnia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Investigations			
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3	3 / 9 (33.33%) 4	5 / 9 (55.56%) 7
Arthropod bite subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 9 (22.22%) 2	0 / 9 (0.00%) 0
Laceration			

subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Torus fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Agitation postoperative			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Postoperative ileus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Tibia fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	4 / 8 (50.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	8	1	0
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Dyslexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Strabismus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	2 / 9 (22.22%)
occurrences (all)	1	2	2
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Nausea			

subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Food poisoning			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lip pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	4 / 9 (44.44%)
occurrences (all)	1	2	5
Joint contracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Scoliosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Arthralgia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pelvic deformity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	4 / 9 (44.44%)	3 / 9 (33.33%)
occurrences (all)	0	5	4
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	1 / 9 (11.11%)
occurrences (all)	3	2	1
Pharyngitis streptococcal			
subjects affected / exposed	3 / 8 (37.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Localised infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Otitis media			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0

Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Eye infection staphylococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Skin bacterial infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Non-serious adverse events	Nusinersen 6 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Puncture site pain			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Catheter site haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Catheter site related reaction			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Chest discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Feeling cold			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gravitational oedema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vessel puncture site haematoma			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Atelectasis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cough			

subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Restrictive pulmonary disease subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all) Dysphoria subjects affected / exposed occurrences (all) Parasomnia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Investigations Blood bicarbonate decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Injury, poisoning and procedural complications Post lumbar puncture syndrome subjects affected / exposed occurrences (all) Arthropod bite	1 / 8 (12.50%) 1		

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Sunburn			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Torus fracture			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Agitation postoperative			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Postoperative ileus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Tibia fracture			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

Nervous system disorders	Respiratory syncytial virus infection		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	
	Headache		
	subjects affected / exposed	2 / 8 (25.00%)	
	occurrences (all)	5	
	Dysgeusia		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	
	Dyslexia		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	
	Hypoaesthesia		
	subjects affected / exposed	1 / 8 (12.50%)	
	occurrences (all)	1	
	Paraesthesia		
	subjects affected / exposed	1 / 8 (12.50%)	
	occurrences (all)	1	
Ear and labyrinth disorders	Ear pain		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	
Eye disorders	Conjunctivitis		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	
	Strabismus		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	
Gastrointestinal disorders	Vomiting		
	subjects affected / exposed	1 / 8 (12.50%)	
	occurrences (all)	1	
	Constipation		
	subjects affected / exposed	0 / 8 (0.00%)	
	occurrences (all)	0	

Nausea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Food poisoning			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hypoaesthesia oral			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lip pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Joint contracture			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Scoliosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Arthralgia			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pelvic deformity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Pharyngitis streptococcal			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Eye infection staphylococcal			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrointestinal viral infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Skin bacterial infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2012	• Changed "SMN2 copy number" to "SMN genetics" and indicated that this includes SMN copy number as well as SMN gene sequencing • Changed Day 2 plasma PK time point from "24 hours" to "20-24 hours" • Updated ISIS 396443-CS1 clinical study results
05 August 2013	• Added an additional cohort of 8 subjects (Cohort 4) to receive 3 doses of 12 mg ISIS 396443 (Days 1, 29, and 85) • Added a 24-hour urine collection for PK analysis on Days 1 and 85 for Cohort 4 subjects • Updated clinical experience section to include the final results from the ISIS 396443-CS1 clinical study and added information on the ISIS 396443-CS12 and ISIS 396443-CS3A clinical studies

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported