



Clinical trial results:

A Phase 2, randomized, double-blind, sham-procedure-controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

Summary

EudraCT number	2014-003657-33
Trial protocol	DE GB
Global end of trial date	24 September 2018

Results information

Result version number	v1
This version publication date	12 April 2019
First version publication date	12 April 2019

Trial information

Trial identification

Sponsor protocol code	232SM202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02462759
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Part 1 of this study was to assess the safety and tolerability of ISIS 396443 in subjects with spinal muscular atrophy (SMA) who were not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. The primary objective of Part 2 of this study was to assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	21
EEA total number of subjects	5

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)	16

Children (2-11 years)	5
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:

Subjects were recruited from sites in the US and Germany. Part 1 was terminated early as positive efficacy results were observed in interim analysis of study 201300442229 and it was considered unethical to continue this part of study. Part 2 was also terminated early to rollover and continue to follow subjects in study 201500187016.

Pre-assignment

Screening details:

A total of 21 subjects with SMA were randomised in Part 1 of the study (7 subjects in sham procedure group, 14 subjects in ISIS 396443 group). One subject died in sham procedure group of Part 1. A total of 20 subjects were enrolled to receive ISIS 396443 in open-label phase of Part 2. Integrated analysis was performed for Part 1 and 2 of the study.

Period 1

Period 1 title	Part 1: Double Blind
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Sham Procedure (Part 1)

Arm description:

Sham procedure on Day 1, 15, 29, 64, 183 and 302.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	ISIS 396443 (Part 1)

Arm description:

Single dose of 9.6 milligrams (mg) to 12.0 mg ISIS 396443, based on subject's age, intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183 and 302.

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

Dosage and administration details:

Single dose of 9.6 mg to 12.0 mg ISIS 396443, based on subject's age, intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183 and 302.

Number of subjects in period 1	Sham Procedure (Part 1)	ISIS 396443 (Part 1)
Started	7	14
Completed	6	14
Not completed	1	0
Death	1	-

Period 2

Period 2 title	Part 2: Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ISIS 396443 (Part 2)
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Arm description:

Subjects who were in Sham procedure group in Part 1, received single dose of 12.0 mg ISIS 396443 intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183, 302, 421, 540, 659 and 778 in Part 2; subjects who were in ISIS 396443 group in Part 1 continued to receive a single dose of 9.6 mg to 12.0 mg ISIS 396443 intrathecal bolus injection maintenance doses on Day 1, 120, 239, 358, 477, 596 and 715 in Part 2.

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

Dosage and administration details:

Subjects who were in Sham procedure group in Part 1, received single dose of 12.0 mg ISIS 396443 intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183, 302, 421, 540, 659 and 778 in Part 2; subjects who were in ISIS 396443 group in Part 1 continued to receive a single dose of 9.6 mg to 12.0 mg ISIS 396443 intrathecal bolus injection maintenance doses on Day 1, 120, 239, 358, 477, 596 and 715 in Part 2.

Number of subjects in period 2	ISIS 396443 (Part 2)
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Sham Procedure (Part 1)
Reporting group description: Sham procedure on Day 1, 15, 29, 64, 183 and 302.	
Reporting group title	ISIS 396443 (Part 1)
Reporting group description: Single dose of 9.6 milligrams (mg) to 12.0 mg ISIS 396443, based on subject's age, intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183 and 302.	

Reporting group values	Sham Procedure (Part 1)	ISIS 396443 (Part 1)	Total
Number of subjects	7	14	21
Age Categorical Units: Subjects			

Age Continuous Units: months arithmetic mean standard deviation	24.42 ± 13.839	19.40 ± 10.115	-
Gender Categorical Units: Subjects			
Female	5	5	10
Male	2	9	11
Ethnicity Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	4	9	13
Not reported due to confidentiality	1	4	5
Race Units: Subjects			
Asian	3	2	5
White	2	7	9
Other	1	1	2
Not reported due to confidentiality	1	4	5

End points

End points reporting groups

Reporting group title	Sham Procedure (Part 1)
Reporting group description: Sham procedure on Day 1, 15, 29, 64, 183 and 302.	
Reporting group title	ISIS 396443 (Part 1)
Reporting group description: Single dose of 9.6 milligrams (mg) to 12.0 mg ISIS 396443, based on subject's age, intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183 and 302.	
Reporting group title	ISIS 396443 (Part 2)
Reporting group description: Subjects who were in Sham procedure group in Part 1, received single dose of 12.0 mg ISIS 396443 intrathecal bolus injection loading doses on Day 1, 15, 29, 64 and maintenance doses, every 4 months, on Day 183, 302, 421, 540, 659 and 778 in Part 2; subjects who were in ISIS 396443 group in Part 1 continued to receive a single dose of 9.6 mg to 12.0 mg ISIS 396443 intrathecal bolus injection maintenance doses on Day 1, 120, 239, 358, 477, 596 and 715 in Part 2.	
Subject analysis set title	Sham Procedure in Part 1
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received single dose of sham procedure on Day 1, 15, 29, 64, 183 and 302 in Part 1 of the study.	
Subject analysis set title	ISIS 396443 in Part 2 (subjects on sham in Part 1)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received single dose of ISIS 396443 on Day 1, 15, 29, 64, 183, 302, 421, 540, 659 and 778 in Part 2.	
Subject analysis set title	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received single dose of ISIS 396443 on Day 1, 15, 29, 64, 183 and 302 in Part 1 of the study and then received single dose of ISIS 396443 on Day 1, 120, 239, 358, 477, 596 and 715 in Part 2 of the study.	

Primary: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
End point description: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A SAE is any untoward medical occurrence that at any dose results in death, life-threatening event, requires inpatient hospitalization, significant disability/incapacity or congenital anomaly. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.	
End point type	Primary
End point timeframe: Part 1 and 2: From first dose/sham procedure to end of study (up to 1080 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: Only descriptive analysis was planned to be reported.

End point values	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	14	
Units: subjects				
AEs	6	6	14	
SAEs	3	4	9	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Change from Baseline in Clinical Laboratory Parameters

End point title	Number of Subjects with Change from Baseline in Clinical Laboratory Parameters ^[2]
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End point description:

Clinically significant changes in blood chemistry, hematology and urinalysis assessments were evaluated. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.

End point type	Primary
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End point timeframe:

Part 1 and 2: From first dose/sham procedure to end of study (up to 1080 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	14	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Change from Baseline in Electrocardiograms (ECGs)

End point title	Number of Subjects with Change from Baseline in Electrocardiograms (ECGs) ^[3]
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End point description:

Clinically significant changes in ECG measurements were evaluated for assessing the safety of ISIS 396443. The safety population included all subjects who were randomised and received at least 1 dose

of study treatment or sham procedure.

End point type	Primary
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End point timeframe:

Part 1: Day 2, 29 and 422; Part 2: Day 1 to 596

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	14	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Change from Baseline in Vital Signs

End point title	Number of Subjects with Change from Baseline in Vital Signs ^[4]
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End point description:

Clinically significant changes in vital signs were evaluated for assessing the safety of ISIS 396443. Vital signs that were assessed included resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.

End point type	Primary
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End point timeframe:

Part 1: Baseline to Day 422; Part 2: Baseline to Day 596

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	14	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Head Circumference

End point title	Change from Baseline in Head Circumference ^[5]
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End point description:

Subjects were analysed for change in growth parameter of head circumference to evaluate clinical efficacy. WHO Child Growth Standards were used to determine the head circumference percentile. Study days were windowed for integrated analysis and labelled as follows: Days ≤ 1 as Baseline; Days > 1 to ≤ 22 as Day 15; Days > 22 to ≤ 47 as Day 29; Days > 47 to ≤ 123 as Day 64; Days > 123 to ≤ 242 as Day 183; Days > 242 to ≤ 362 as Day 302; Days > 362 to ≤ 482 as Day 422; Days > 482 to ≤ 600 as Day 540; Days > 600 to ≤ 719 as Day 659; Days > 719 to ≤ 838 as Day 778; Days > 838 to ≤ 958 as Day 898; Days > 958 to ≤ 1078 as Day 1018; Days > 1078 to ≤ 1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.

End point type	Primary
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End point timeframe:

Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: centimetre (cm)				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	50.8 (\pm 3.83)	47.3 (\pm 1.51)		
Change at Day 15 (n=5,14)	-0.7 (\pm 3.34)	0.1 (\pm 0.36)		
Change at Day 29 (n=6,13)	0.0 (\pm 2.76)	0.3 (\pm 0.65)		
Change at Day 64 (n=6,14)	0.1 (\pm 2.64)	0.5 (\pm 0.73)		
Change at Day 183 (n=6,14)	0.3 (\pm 3.10)	1.0 (\pm 1.12)		
Change at Day 302 (n=6,14)	1.0 (\pm 3.28)	1.6 (\pm 1.05)		
Change at Day 422 (n=6,13)	0.9 (\pm 2.47)	2.0 (\pm 1.24)		
Change at Day 540 (n=6,14)	1.3 (\pm 1.97)	2.5 (\pm 1.24)		
Change at Day 659 (n=6,14)	1.5 (\pm 2.53)	2.6 (\pm 1.37)		
Change at Day 778 (n=0,14)	99999 (\pm 99999)	2.8 (\pm 0.92)		
Change at Day 898 (n=0,12)	99999 (\pm 99999)	3.5 (\pm 1.05)		
Change at Day 1018 (n=0,5)	99999 (\pm 99999)	3.5 (\pm 2.06)		
Change at Day 1138 (n=0,1)	99999 (\pm 99999)	4.0 (\pm 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Chest Circumference

End point title	Change from Baseline in Chest Circumference ^[6]
End point description:	
Subjects were analysed for change in growth parameter of chest circumference to evaluate clinical efficacy. WHO Child Growth Standards were used to determine the chest circumference percentile. Study days were windowed for integrated analysis and labelled as follows: Days ≤1 as Baseline; Days >1 to ≤22 as Day 15; Days >22 to ≤47 as Day 29; Days >47 to ≤123 as Day 64; Days >123 to ≤242 as Day 183; Days >242 to ≤362 as Day 302; Days >362 to ≤482 as Day 422; Days >482 to ≤600 as Day 540; Days >600 to ≤719 as Day 659; Days >719 to ≤838 as Day 778; Days >838 to ≤958 as Day 898; Days >958 to ≤1078 as Day 1018; Days >1078 to ≤1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.	
End point type	Primary
End point timeframe:	
Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138	
Notes:	
[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Only descriptive analysis was planned to be reported.	

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	51.3 (± 5.45)	46.9 (± 3.91)		
Change at Day 15 (n=5,14)	-0.2 (± 3.86)	-0.4 (± 1.53)		
Change at Day 29 (n=6,13)	-1.1 (± 2.70)	0.2 (± 1.39)		
Change at Day 64 (n=6,14)	-0.9 (± 3.50)	0.2 (± 1.92)		
Change at Day 183 (n=6,14)	0.2 (± 3.04)	1.4 (± 2.02)		
Change at Day 302 (n=6,14)	1.2 (± 3.07)	1.6 (± 2.86)		
Change at Day 422 (n=6,14)	0.5 (± 3.72)	2.8 (± 2.73)		
Change at Day 540 (n=6,14)	1.8 (± 2.42)	3.8 (± 3.23)		
Change at Day 659 (n=6,14)	2.9 (± 3.85)	5.1 (± 3.29)		
Change at Day 778 (n=0,14)	99999 (± 99999)	5.5 (± 3.52)		
Change at Day 898 (n=0,12)	99999 (± 99999)	7.1 (± 3.04)		
Change at Day 1018 (n=0,5)	99999 (± 99999)	9.7 (± 4.92)		
Change at Day 1138 (n=0,1)	99999 (± 99999)	9.1 (± 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Arm Circumference

End point title	Change from Baseline in Arm Circumference ^[7]
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End point description:

Subjects were analysed for change in growth parameter of arm circumference to evaluate clinical efficacy. WHO Child Growth Standards were used to determine the arm circumference percentile. Study days were windowed for integrated analysis and labelled as follows: Days ≤ 1 as Baseline; Days > 1 to ≤ 22 as Day 15; Days > 22 to ≤ 47 as Day 29; Days > 47 to ≤ 123 as Day 64; Days > 123 to ≤ 242 as Day 183; Days > 242 to ≤ 362 as Day 302; Days > 362 to ≤ 482 as Day 422; Days > 482 to ≤ 600 as Day 540; Days > 600 to ≤ 719 as Day 659; Days > 719 to ≤ 838 as Day 778; Days > 838 to ≤ 958 as Day 898; Days > 958 to ≤ 1078 as Day 1018; Days > 1078 to ≤ 1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.

End point type	Primary
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End point timeframe:

Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	16.2 (\pm 1.19)	14.5 (\pm 1.85)		
Change at Day 15 (n=5,14)	-0.4 (\pm 1.04)	0.3 (\pm 0.61)		
Change at Day 29 (n=6,13)	-0.5 (\pm 1.08)	-0.1 (\pm 0.54)		
Change at Day 64 (n=6,14)	-0.3 (\pm 0.49)	-0.4 (\pm 0.89)		
Change at Day 183 (n=6,14)	0.0 (\pm 0.89)	0.0 (\pm 0.85)		
Change at Day 302 (n=6,14)	-0.6 (\pm 0.89)	0.2 (\pm 1.17)		
Change at Day 422 (n=6,14)	-0.6 (\pm 1.82)	0.5 (\pm 1.71)		
Change at Day 540 (n=6,14)	-0.2 (\pm 2.24)	0.5 (\pm 1.89)		
Change at Day 659 (n=6,14)	0.6 (\pm 0.93)	0.6 (\pm 1.93)		
Change at Day 778 (n=0,14)	99999 (\pm 99999)	0.0 (\pm 2.18)		
Change at Day 898 (n=0,12)	99999 (\pm 99999)	0.8 (\pm 2.70)		
Change at Day 1018 (n=0,5)	99999 (\pm 99999)	1.0 (\pm 2.02)		
Change at Day 1138 (n=0,1)	99999 (\pm 99999)	1.5 (\pm 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Weight for Age

End point title	Change from Baseline in Weight for Age ^[8]
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End point description:

Subjects were analysed for change in growth parameter of weight for age to evaluate clinical efficacy.

WHO Child Growth Standards were used to determine the head circumference percentile. Study days were windowed for integrated analysis and labelled as follows: Days ≤1 as Baseline; Days >1 to ≤22 as Day 15; Days >22 to ≤47 as Day 29; Days >47 to ≤123 as Day 64; Days >123 to ≤242 as Day 183; Days >242 to ≤362 as Day 302; Days >362 to ≤482 as Day 422; Days >482 to ≤600 as Day 540; Days >600 to ≤719 as Day 659; Days >719 to ≤838 as Day 778; Days >838 to ≤958 as Day 898; Days >958 to ≤1078 as Day 1018; Days >1078 to ≤1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.

End point type	Primary
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End point timeframe:

Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	42.5 (± 40.87)	25.3 (± 28.41)		
Change at Day 15 (n=6,14)	-1.3 (± 1.41)	3.6 (± 12.12)		
Change at Day 29 (n=6,14)	-2.4 (± 1.61)	-1.4 (± 4.82)		
Change at Day 64 (n=6,14)	-2.9 (± 2.58)	0.5 (± 8.17)		
Change at Day 183 (n=6,14)	-3.8 (± 6.93)	-5.9 (± 8.73)		
Change at Day 302 (n=6,14)	-10.1 (± 13.04)	-8.0 (± 15.42)		
Change at Day 422 (n=6,14)	-6.3 (± 9.45)	-7.5 (± 17.52)		
Change at Day 540 (n=6,14)	-7.0 (± 6.56)	-8.1 (± 17.26)		
Change at Day 659 (n=6,14)	-8.5 (± 17.64)	-10.5 (± 22.23)		
Change at Day 778 (n=0,14)	99999 (± 99999)	-13.2 (± 16.95)		
Change at Day 898 (n=0,12)	99999 (± 99999)	-10.5 (± 24.10)		
Change at Day 1018 (n=0,5)	99999 (± 99999)	-7.0 (± 34.14)		
Change at Day 1138 (n=0,1)	99999 (± 99999)	0.3 (± 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Weight for Length

End point title	Change from Baseline in Weight for Length ^[9]
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End point description:

Subjects were analysed for change in growth parameter of weight for length to evaluate clinical efficacy.

WHO Child Growth Standards were used to determine the weight for length percentile. Study days were windowed for integrated analysis and labelled as follows: Days ≤1 as Baseline; Days >1 to ≤ 22 as Day 15; Days >22 to ≤47 as Day 29; Days >47 to ≤ 123 as Day 64; Days >123 to ≤242 as Day 183; Days >242 to ≤362 as Day 302; Days >362 to ≤482 as Day 422; Days >482 to ≤ 600 as Day 540; Days >600 to ≤ 719 as Day 659; Days >719 to ≤ 838 as Day 778; Days >838 to ≤ 958 as Day 898; Days >958 to ≤ 1078 as Day 1018; Days >1078 to ≤ 1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.

End point type	Primary
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End point timeframe:

Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	13.0 (± 2.00)	9.5 (± 1.37)		
Change at Day 15 (n=6,14)	-0.1 (± 0.23)	0.2 (± 0.44)		
Change at Day 29 (n=6,14)	-0.1 (± 0.26)	0.1 (± 0.23)		
Change at Day 64 (n=6,14)	0.0 (± 0.39)	0.4 (± 0.42)		
Change at Day 183 (n=6,14)	0.8 (± 0.61)	0.7 (± 0.48)		
Change at Day 302 (n=6,14)	0.7 (± 1.04)	1.3 (± 0.87)		
Change at Day 422 (n=6,14)	1.8 (± 1.03)	1.9 (± 1.02)		
Change at Day 540 (n=6,14)	2.3 (± 1.33)	2.2 (± 1.17)		
Change at Day 659 (n=6,14)	3.1 (± 1.39)	2.8 (± 1.41)		
Change at Day 778 (n=0,14)	99999 (± 99999)	3.2 (± 1.87)		
Change at Day 898 (n=0,12)	99999 (± 99999)	3.9 (± 2.86)		
Change at Day 1018 (n=0,5)	99999 (± 99999)	4.3 (± 1.96)		
Change at Day 1138 (n=0,1)	99999 (± 99999)	5.0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Head to Chest Circumference (HCC) Ratio

End point title	Change from Baseline in Head to Chest Circumference (HCC) Ratio ^[10]
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End point description:

Subjects were analysed for change in growth parameter of HCC to evaluate clinical efficacy. WHO Child Growth Standards were used to determine the HCC circumference percentile. Study days were

windowed for integrated analysis and labelled as follows: Days ≤1 as Baseline; Days >1 to ≤22 as Day 15; Days >22 to ≤47 as Day 29; Days >47 to ≤123 as Day 64; Days >123 to ≤242 as Day 183; Days >242 to ≤362 as Day 302; Days >362 to ≤482 as Day 422; Days >482 to ≤600 as Day 540; Days >600 to ≤719 as Day 659; Days >719 to ≤838 as Day 778; Days >838 to ≤958 as Day 898; Days >958 to ≤1078 as Day 1018; Days >1078 to ≤1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.

End point type	Primary
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End point timeframe:

Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	1.0 (± 0.05)	1.0 (± 0.08)		
Change at Day 15 (n=5,14)	0.0 (± 0.03)	0.0 (± 0.03)		
Change at Day 29 (n=6,13)	0.0 (± 0.04)	0.0 (± 0.04)		
Change at Day 64 (n=6,14)	0.0 (± 0.04)	0.0 (± 0.05)		
Change at Day 183 (n=6,14)	0.0 (± 0.05)	0.0 (± 0.05)		
Change at Day 302 (n=6,14)	0.0 (± 0.03)	0.0 (± 0.06)		
Change at Day 422 (n=6,13)	0.0 (± 0.04)	0.0 (± 0.06)		
Change at Day 540 (n=6,14)	0.0 (± 0.03)	0.0 (± 0.06)		
Change at Day 659 (n=6,14)	0.0 (± 0.03)	-0.1 (± 0.06)		
Change at Day 778 (n=0,14)	99999 (± 99999)	-0.1 (± 0.07)		
Change at Day 898 (n=0,12)	99999 (± 99999)	-0.1 (± 0.06)		
Change at Day 1018 (n=0,5)	99999 (± 99999)	-0.1 (± 0.10)		
Change at Day 1138 (n=0,1)	99999 (± 99999)	-0.1 (± 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Body Length

End point title	Change from Baseline in Body Length ^[11]
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End point description:

Subjects were analysed for change in growth parameter of body length to evaluate clinical efficacy. WHO Child Growth Standards were used to determine the body length percentile. Study days were windowed for integrated analysis and labelled as follows: Days ≤1 as Baseline; Days >1 to ≤22 as Day 15; Days >22 to ≤47 as Day 29; Days >47 to ≤123 as Day 64; Days >123 to ≤242 as Day

183;Days >242 to <=362 as Day 302;Days >362 to <=482 as Day 422;Days >482 to <= 600 as Day 540;Days >600 to <= 719 as Day 659;Days >719 to <= 838 as Day 778;Days >838 to <= 958 as Day 898;Days >958 to <= 1078 as Day 1018;Days >1078 to <= 1198 as Day 1138. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here "99999" denotes that data was not evaluable at the given time point for the analysis set ISIS 396443 in Part 2 (subjects on sham in Part 1). "n" is the number of subjects evaluated at specified time point.

End point type	Primary
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End point timeframe:

Part 2: Baseline, Day 15, 29, 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=6,14)	95.0 (± 9.48)	79.9 (± 5.25)		
Change at Day 15 (n=5,14)	-1.6 (± 3.19)	-0.1 (± 1.81)		
Change at Day 29 (n=6,13)	-0.9 (± 3.49)	0.9 (± 1.66)		
Change at Day 64 (n=6,14)	0.5 (± 4.77)	1.8 (± 2.40)		
Change at Day 183 (n=6,14)	3.0 (± 4.16)	5.6 (± 2.36)		
Change at Day 302 (n=6,14)	2.9 (± 5.76)	7.1 (± 2.70)		
Change at Day 422 (n=6,14)	4.2 (± 5.42)	9.3 (± 3.09)		
Change at Day 540 (n=6,14)	4.6 (± 7.18)	11.6 (± 3.93)		
Change at Day 659 (n=6,14)	10.8 (± 4.12)	13.1 (± 3.79)		
Change at Day 778 (n=0,14)	99999 (± 99999)	14.8 (± 3.94)		
Change at Day 898 (n=0,12)	99999 (± 99999)	17.2 (± 5.62)		
Change at Day 1018 (n=0,5)	99999 (± 99999)	19.0 (± 6.67)		
Change at Day 1138 (n=0,1)	99999 (± 99999)	15.8 (± 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Change from Baseline in Neurological Examination Outcomes

End point title	Number of Subjects with Change from Baseline in Neurological Examination Outcomes ^[12]
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End point description:

Neurological examinations included assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, reflexes, mood, speech/language and hearing. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.

End point type	Primary
End point timeframe:	
Part 1: Baseline to Day 422; Part 2: Baseline to Day 596	
Notes:	
[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Only descriptive analysis was planned to be reported.	

End point values	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	14	
Units: subjects				
Mental Status	0	1	3	
Level of consciousness	0	1	2	
Sensory function	0	0	0	
Motor function	0	0	0	
Cranial nerve function: Eye Movement	0	0	1	
Cranial nerve function: Vision	0	0	1	
Reflexes	0	0	0	
Mood	5	5	12	
Speech/Language	0	1	1	
Hearing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Change From Baseline in Activated Partial Thromboplastin Time [aPTT]

End point title	Number of Subjects with Change From Baseline in Activated Partial Thromboplastin Time [aPTT] ^[13]
End point description:	
Activated partial thromboplastin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of aPTT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of aPTT at baseline to high values postbaseline. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here 'n' is the number of subjects whose baseline value was not low (or high) and who had at least one post-baseline.	
End point type	Primary
End point timeframe:	
Part 2: Up to 1080 days	
Notes:	
[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Only descriptive analysis was planned to be reported.	

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: subjects				
Shift to Low (n=6,9)	0	0		
Shift to High (n=6,10)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Change From Baseline in Partial Thromboplastin Time [PTT]

End point title	Number of Subjects with Change From Baseline in Partial Thromboplastin Time [PTT] ^[14]
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End point description:

PTT was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of PTT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of PTT at baseline to high values postbaseline. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here 'n' is the number of subjects whose baseline value was not low (or high) and who had at least one post-baseline value.

End point type	Primary
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End point timeframe:

Part 2: Up to 1080 days

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: subjects				
Shift to Low (n=5,6)	0	0		
Shift to High (n=5,6)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Change From Baseline in International Normalized Ratio [INR])

End point title	Number of Subjects With Change From Baseline in International Normalized Ratio [INR] ^[15]
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End point description:

INR was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of INR at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of INR at baseline to high values postbaseline. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure. Here 'n' is the number of subjects whose baseline value was not low (or high) and who had at least one post-baseline value.

End point type	Primary
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End point timeframe:

Part 2: Up to 1080 days

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: subjects				
Shift to Low (n=4,7)	0	0		
Shift to High (n=4,7)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Presence of Urine Total Protein Post-baseline

End point title	Number of Subjects With Presence of Urine Total Protein Post-baseline ^[16]
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End point description:

Urine total protein was evaluated to assess safety. The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.

End point type	Primary
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End point timeframe:

Part 2: Up to 1080 days

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: subjects				

Baseline	0	1		
High/Postive	2	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of ISIS 396443 in Part 2 of Study in Subjects who Received Sham Procedure in Part 1 of the Study

End point title	Plasma Concentration of ISIS 396443 in Part 2 of Study in Subjects who Received Sham Procedure in Part 1 of the Study
End point description:	Study days were windowed for integrated analysis and labelled as follows: Days >47 to <= 123 as Day 64; Days >123 to <=242 as Day 183; Days >482 to <= 600 as Day 540; Days >600 to <= 719 as Day 659. The pharmacokinetic (PK) population included all subjects who were randomised and have at least 1 evaluable post dose or post sham-procedure PK sample.
End point type	Secondary
End point timeframe:	Pre-dose on Days 64, 183, 540 and 659

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Day 64	1.983 (± 0.7320)			
Day 183	0.776 (± 0.3994)			
Day 540	0.425 (± 0.2200)			
Day 659	0.365 (± 0.1146)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of ISIS 396443 in Part 1 and 2 of Study in Subjects who Received ISIS 396443 in Part 1 of the Study

End point title	Plasma Concentration of ISIS 396443 in Part 1 and 2 of Study in Subjects who Received ISIS 396443 in Part 1 of the Study
End point description:	Study days were windowed for integrated analysis and labelled as follows: Days >47 to <= 123 as Day

64;Days >123 to <=242 as Day 183;Days >242 to <=362 as Day 302;Days >362 to <=482 as Day 422;Days >482 to <= 600 as Day 540;Days >600 to <= 719 as Day 659;Days >719 to <= 838 as Day 778;Days >838 to <= 958 as Day 898;Days >958 to <= 1078 as Day 1018;Days >1078 to <= 1198 as Day 1138. The PK population included all subjects who were randomised and have at least 1 evaluable post dose or post sham-procedure PK sample. Here "n" is the number of subjects evaluated at the specified time point.

End point type	Secondary
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End point timeframe:

Pre-dose on Days 64, 183, 302, 422, 540, 659, 778, 898, 1018 and 1138

End point values	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 64 (n=14)	2.139 (± 0.8811)			
Day 183 (n=13)	1.059 (± 0.5569)			
Day 302 (n=5)	0.667 (± 0.1852)			
Day 422 (n=9)	0.858 (± 0.4636)			
Day 540 (n=5)	0.608 (± 0.2736)			
Day 659 (n=9)	0.739 (± 0.2812)			
Day 778 (n=5)	0.590 (± 0.3414)			
Day 898 (n=10)	0.661 (± 0.2558)			
Day 1018 (n=4)	0.329 (± 0.1020)			
Day 1138 (n=1)	0.423 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal Fluid (CSF) Concentration of ISIS 396443 in Part 2 of Study in Subjects who Received Sham Procedure in Part 1 of the Study

End point title	Cerebrospinal Fluid (CSF) Concentration of ISIS 396443 in Part 2 of Study in Subjects who Received Sham Procedure in Part 1 of the Study
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End point description:

CSF samples were analysed for ISIS 396443 concentrations in subjects. Study days were windowed for integrated analysis and labelled as follows: Days >1 to <= 22 as Day 15;Days >22 to <=47 as Day 29;Days >47 to <= 123 as Day 64;Days >123 to <=242 as Day 183;Days >242 to <=362 as Day 302;Days >362 to <=482 as Day 422;Days >482 to <= 600 as Day 540. The PK population included all subjects who were randomised and have at least 1 evaluable post dose or post sham-procedure PK

sample. Here "99999" denotes that mean was below the lower limit of quantification (LLOQ) hence standard deviation was not evaluated. LLOQ is 50 picogram per millilitre. "n" is the number of subjects evaluated at the specified time point.

End point type	Secondary
End point timeframe:	
Pre-dose on Days 15, 29, 64, 183, 302, 422 and 540	

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=5)	99999 (± 99999)			
Day 15 (n=5)	3.094 (± 1.2172)			
Day 29 (n=6)	4.805 (± 2.6706)			
Day 64 (n=6)	4.357 (± 2.3229)			
Day 183 (n=6)	4.110 (± 2.4535)			
Day 302 (n=6)	5.397 (± 2.7503)			
Day 422 (n=6)	6.460 (± 2.9428)			
Day 540 (n=6)	8.405 (± 6.2423)			

Statistical analyses

No statistical analyses for this end point

Secondary: CSF Concentration of ISIS 396443 in Part 1 and 2 of Study in Subjects who Received ISIS 396443 in Part 1 of the Study

End point title	CSF Concentration of ISIS 396443 in Part 1 and 2 of Study in Subjects who Received ISIS 396443 in Part 1 of the Study
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End point description:

CSF samples were analysed for ISIS 396443 concentrations in subjects. Study days were windowed for integrated analysis and labelled as follows: Days >1 to ≤ 22 as Day 15; Days >22 to ≤ 47 as Day 29; Days >47 to ≤ 123 as Day 64; Days >123 to ≤ 242 as Day 183; Days >242 to ≤ 362 as Day 302; Days >362 to ≤ 482 as Day 422; Days >482 to ≤ 600 as Day 540; Days >600 to ≤ 719 as Day 659; Days >719 to ≤ 838 as Day 778; Days >838 to ≤ 958 as Day 898; Days >958 to ≤ 1078 as Day 1018. The PK population included all subjects who were randomised and have at least 1 evaluable post dose or post sham-procedure PK sample. Here "99999" denotes that mean was below the lower limit of quantification (LLOQ) hence standard deviation was not evaluated. LLOQ is 50 picogram per millilitre. "n" is the number of subjects evaluated at the specified time point.

End point type	Secondary
End point timeframe:	
Pre-dose on Days 15, 29, 64, 183, 302, 422, 540, 659, 778, 898 and 1018	

End point values	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=8)	99999 (± 99999)			
Day 15 (n=13)	3.925 (± 2.0525)			
Day 29 (n=14)	7.273 (± 4.4786)			
Day 64 (n=14)	7.176 (± 2.8487)			
Day 183 (n=14)	8.226 (± 3.6450)			
Day 302 (n=13)	8.968 (± 3.1188)			
Day 422 (n=13)	9.251 (± 4.0631)			
Day 540 (n=14)	9.026 (± 2.6864)			
Day 659 (n=14)	9.785 (± 3.3725)			
Day 778 (n=13)	8.632 (± 2.4131)			
Day 898 (n=8)	11.321 (± 8.9351)			
Day 1018 (n=1)	7.010 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Plasma Antibodies to ISIS 396443

End point title	Number of Subjects with Plasma Antibodies to ISIS 396443
End point description: The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.	
End point type	Secondary
End point timeframe: Part 2: Baseline to Day 596	

End point values	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	14		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start to end of study (up to 1133 days)

Adverse event reporting additional description:

The safety population included all subjects who were randomised and received at least 1 dose of study treatment or sham procedure.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Sham Procedure in Part 1
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Reporting group description:

Subjects who received single dose of sham procedure on Day 1, 15, 29, 64, 183 and 302 in Part 1 of the study.

Reporting group title	ISIS 396443 in Part 2 (subjects on sham in Part 1)
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Reporting group description:

Subjects who received single dose of ISIS 396443 on Day 1, 15, 29, 64, 183, 302, 421, 540, 659 and 778 in Part 2.

Reporting group title	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)
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Reporting group description:

Subjects who received single dose of ISIS 396443 on Day 1, 15, 29, 64, 183 and 302 in Part 1 of the study and then received single dose of ISIS 396443 on Day 1, 120, 239, 358, 477, 596 and 715 in Part 2 of the study.

Serious adverse events	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	4 / 6 (66.67%)	9 / 14 (64.29%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (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
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (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
Loss of consciousness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (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
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial secretion retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	3 / 14 (21.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Bronchiolitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 7 (14.29%) 0 / 1 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 14 (0.00%) 0 / 0 0 / 0
Bronchitis moraxella subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 6 (16.67%) 0 / 2 0 / 0	0 / 14 (0.00%) 0 / 0 0 / 0
Enterovirus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 7 (14.29%) 0 / 1 0 / 0	1 / 6 (16.67%) 0 / 1 0 / 0	0 / 14 (0.00%) 0 / 0 0 / 0
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 6 (16.67%) 0 / 1 0 / 0	1 / 14 (7.14%) 0 / 1 0 / 0
Gastroenteritis norovirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	1 / 14 (7.14%) 0 / 1 0 / 0
Gastroenteritis viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	2 / 14 (14.29%) 0 / 2 0 / 0
Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	1 / 14 (7.14%) 0 / 1 0 / 0
Parainfluenzae virus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 6 (16.67%) 0 / 1 0 / 0	1 / 14 (7.14%) 0 / 1 0 / 0
Pneumonia			

subjects affected / exposed	0 / 7 (0.00%)	3 / 6 (50.00%)	7 / 14 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia moraxella			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			

subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Sham Procedure in Part 1	ISIS 396443 in Part 2 (subjects on sham in Part 1)	ISIS 396443 in Part 1 & 2 (subjects on ISIS 396443 in Part 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	6 / 6 (100.00%)	14 / 14 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	2
Hypertension			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 14 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Complication associated with device subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Fatigue subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Influenza like illness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 14 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 2
Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	4 / 6 (66.67%) 16	12 / 14 (85.71%) 60
Swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Immune system disorders			
Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Reproductive system and breast disorders			

Penile adhesion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Respiratory, thoracic and mediastinal disorders			
Aspiration subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0
Atelectasis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 3	2 / 14 (14.29%) 2
Bronchial secretion retention subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 14 (0.00%) 0
Chronic respiratory failure subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Cough subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	3 / 6 (50.00%) 13	11 / 14 (78.57%) 31
Dysphonia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Dyspnoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 14 (0.00%) 0
Hypoventilation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hypoxia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3	0 / 6 (0.00%) 0	3 / 14 (21.43%) 3
Increased bronchial secretion			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Larynx irritation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract congestion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	4	3
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	6 / 14 (42.86%)
occurrences (all)	0	7	12
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Pneumonia aspiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pulmonary congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Restrictive pulmonary disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	6 / 14 (42.86%)
occurrences (all)	0	4	16
Sinus congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Sleep apnoea syndrome			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Tachypnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	5
Tonsillar hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Upper-airway cough syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Use of accessory respiratory muscles			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Psychiatric disorders			
Dysphemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Intermittent explosive disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Product issues			
Device extrusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Investigations			
Aspiration bronchial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bone density decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Carnitine decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Enterobacter test positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Full blood count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	3
Oxygen saturation decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	0	2	4
Pco2 increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urine output decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urine output increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
White blood cell count increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Incision site erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Incision site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Joint dislocation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 14 (21.43%)
occurrences (all)	0	0	3
Laceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Procedural pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 14 (21.43%)
occurrences (all)	0	0	3
Procedural vomiting			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Stoma site haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Stoma site hypergranulation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Upper limb fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vaccination complication			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Congenital nystagmus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Plagiocephaly			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Tachycardia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 6 (0.00%) 0	3 / 14 (21.43%) 4
Nervous system disorders Cranial nerve disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Dysarthria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	1 / 14 (7.14%) 1
Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Leukocytosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Eye disorders Myopia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1

Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	4 / 14 (28.57%) 4
Dental caries subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	5 / 14 (35.71%) 8
Dyspepsia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 14 (0.00%) 0
Dysphagia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Flatulence subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gingival pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lip swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oral contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Teething			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	2
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	7 / 14 (50.00%)
occurrences (all)	2	2	20
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	3

Miliaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3
Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	5
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	0	3	2
Hip deformity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Joint contracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Joint hyperextension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Muscle tightness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Osteopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	6 / 14 (42.86%)
occurrences (all)	0	2	6

Scoliosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 14 (28.57%)
occurrences (all)	0	0	5
Spinal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Tendinous contracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Torticollis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 14 (28.57%)
occurrences (all)	0	0	4
Conjunctivitis bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	6
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	5 / 14 (35.71%)
occurrences (all)	0	0	5
Gastroenteritis adenovirus			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastroenteritis norovirus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	5 / 14 (35.71%)
occurrences (all)	0	2	7
Otitis externa			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Otitis media acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Parainfluenzae virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	7 / 14 (50.00%)
occurrences (all)	0	2	12
Pneumonia haemophilus			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pneumonia moraxella			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	3 / 14 (21.43%)
occurrences (all)	0	1	3
Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	5 / 14 (35.71%)
occurrences (all)	2	1	13
Rhinovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Stoma site infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	9 / 14 (64.29%)
occurrences (all)	2	10	22
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Vaginal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Viral rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	5 / 14 (35.71%)
occurrences (all)	1	2	14
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2
Dehydration subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	3 / 14 (21.43%) 5
Failure to thrive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Feeding disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hyperchloraemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hypochloraemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1
Hypophagia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 14 (14.29%) 3

Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Weight gain poor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2016	The protocol was amended to add an open-label extension (OLE) Part 2 phase to provide subjects with SMA the opportunity to receive open-label ISIS 396443 for up to 24 months (or until availability of commercial product) in the event that Part 1 of the study was terminated early (based on emergent data from the ISIS 396443 clinical development program).
01 June 2016	The Schedule of Assessments for Parts 1 and 2 of the study was updated.
16 June 2017	The protocol was amended to add safety laboratory assessments for coagulation parameters and renal toxicity as well as efficacy growth parameters. The language regarding the approval of nusinersen in the US and Europe was updated. The Schedule of Events tables were updated to include a window for telephone calls for safety follow up and to make consistent with the rest of the protocol.

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.

Despite the early termination of both Parts of the study, the data from this study is of quality and reliable.

Notes: