



## Clinical trial results:

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

#### Summary

EudraCT number	2014-001947-18
Trial protocol	DE GB SE ES IT FR
Global end of trial date	20 February 2017

#### Results information

Result version number	v1 (current)
This version publication date	06 September 2017
First version publication date	06 September 2017

#### Trial information

##### Trial identification

Sponsor protocol code	ISIS 396443-CS4
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02865109
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, +1 866-633-4636, 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-PIP13-02
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	20 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2017
Global end of trial reached?	Yes
Global end of trial date	20 February 2017
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to examine the clinical efficacy of nusinersen (ISIS 396443) administered intrathecally to participants with later-onset Spinal Muscular Atrophy (SMA). The secondary objective is to examine the safety and tolerability of nusinersen administered intrathecally to participants with later-onset SMA.

Protection of trial subjects:

Written informed consent was obtained from the parent or legal guardian of the subject and, in cases where institutional guidelines and the subject's age dictate, informed assent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study treatment was administered. Sufficient time was given to consider whether to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 65
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Sweden: 2
Worldwide total number of subjects	126
EEA total number of subjects	42

Notes:

<b>Subjects enrolled per age group</b>	
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)	126
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

After parental informed consent was obtained and prior to any treatment, participants entered a Screening Period of up to 21 days to determine their eligibility for the study. Of the 179 participants screened, 53 were screening failures.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Sham procedure

Arm description:

Sham comparator on Days 1, 29, 85 and 274.

Arm type	Sham procedure
No investigational medicinal product assigned in this arm	

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

Nusinersen 12 mg solution via intrathecal (IT) injection on Days 1, 29, 85 and 274.

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

Dosage and administration details:

Nusinersen 12 mg solution via intrathecal (IT) injection on Days 1, 29, 85 and 274.

Number of subjects in period 1	Sham procedure	Nusinersen
Started	42	84
Completed Treatment	42	83 <sup>[1]</sup>
Completed	42	84

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 1 participant completed the study but did not complete treatments due to early study closure

## Baseline characteristics

### Reporting groups

Reporting group title	Sham procedure
Reporting group description: Sham comparator on Days 1, 29, 85 and 274.	
Reporting group title	Nusinersen
Reporting group description: Nusinersen 12 mg solution via intrathecal (IT) injection on Days 1, 29, 85 and 274.	

Reporting group values	Sham procedure	Nusinersen	Total
Number of subjects	42	84	126
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)	42	84	126
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	3.4	3.8	-
standard deviation	± 1.61	± 1.63	-
Gender, Male/Female Units: Subjects			
Female	21	46	67
Male	21	38	59
Study Specific Characteristic   Hammersmith Functional Motor Scale - Expanded (HFMSE) Score			
The HFMSE consists of 33 scored activities used to assess motor function in children with SMA. Participants were asked to do a specific activity (such as rolling) and they were then graded on the quality and execution of that movement on a scale of 0=being unable, 1=performed with some compensation, and 2=unaided. The overall score is the sum of the scores for all activities with a maximum achievable score of 66. Higher scores indicate increased motor function.			
Units: scores on a scale			
arithmetic mean	19.9	22.4	-
standard deviation	± 7.23	± 8.33	-

## End points

### End points reporting groups

Reporting group title	Sham procedure
Reporting group description: Sham comparator on Days 1, 29, 85 and 274.	
Reporting group title	Nusinersen
Reporting group description: Nusinersen 12 mg solution via intrathecal (IT) injection on Days 1, 29, 85 and 274.	

### Primary: Change from Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) Score at Month 15

End point title	Change from Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) Score at Month 15
End point description: The HFMSE consists of 33 scored activities used to assess motor function in children with SMA. The scale was originally developed with 20 scored activities and was devised for use in children with SMA Type 2 and Type 3 with limited ambulation to give objective information on motor ability and clinical progression. The expanded scale includes an additional module of 13 items developed to allow for evaluation of ambulatory SMA patients. Participants were asked to do a specific activity (such as rolling) and they were then graded on the quality and execution of that movement on a scale of 0=being unable, 1=performed with some compensation, and 2=unaided. The overall score is the sum of the scores for all activities with a maximum achievable score of 66. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement.	
End point type	Primary
End point timeframe: Baseline and Month 15	

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	84		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-1 (-2.5 to 0.5)	3.9 (3 to 4.9)		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Nusinersen v Sham procedure

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 1E-7 <sup>[2]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	0.91

Notes:

[1] - ITT Set: All participants who were randomized and received at least 1 dose of study drug/sham procedure. Missing postbaseline HFMSE data were imputed using multiple imputation.

[2] - ANCOVA model with treatment group as a factor and age at Screening and baseline HFMSE score as covariates. Missing postbaseline HFMSE data were imputed using multiple imputation.

### Secondary: Percentage of Participants Who Achieved a 3-Point Increase from Baseline in HFMSE Score at Month 15

End point title	Percentage of Participants Who Achieved a 3-Point Increase from Baseline in HFMSE Score at Month 15
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End point description:

The HFMSE consists of 33 scored activities used to assess motor function in children with SMA. The scale was originally developed with 20 scored activities and was devised for use in children with SMA Type 2 and Type 3 with limited ambulation to give objective information on motor ability and clinical progression. The expanded scale includes an additional module of 13 items developed to allow for evaluation of ambulatory SMA patients. Participants were asked to do a specific activity (such as rolling) and they were then graded on the quality and execution of that movement on a scale of 0=being unable, 1=performed with some compensation, and 2=unaided. The overall score is the sum of the scores for all activities with a maximum achievable score of 66. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline and Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	84		
Units: percentage of participants				
number (confidence interval 95%)	26.3 (12.4 to 40.22)	56.8 (45.62 to 68.05)		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sham procedure v Nusinersen

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.0006 <sup>[4]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	14.91

Notes:

[3] - ITT Set: All participants who were randomized and received at least 1 dose of study drug/sham procedure. Missing postbaseline HFMSE data were imputed using multiple imputation.

[4] - Based on logistic regression with treatment effect and adjustment for each participant's age at screening and HFMSE score at baseline. Missing postbaseline HFMSE data were imputed using multiple imputation.

<b>Statistical analysis title</b>	Statistical Analysis 2
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Statistical analysis description:

Difference in proportions of Nusinersen minus Sham Procedure are from the MI procedure and are based on binomial proportions.

Comparison groups	Sham procedure v Nusinersen
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
Parameter estimate	Difference in Proportions
Point estimate	30.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.74
upper limit	48.31

Notes:

[5] - ITT Set: All participants who were randomized and received at least 1 dose of study drug/sham procedure. Missing postbaseline HFMSE data were imputed using the MI.

## **Secondary: Percentage of Participants that Achieved any New Motor Milestone at Month 15**

End point title	Percentage of Participants that Achieved any New Motor Milestone at Month 15
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End point description:

New motor milestones are defined as sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone.

End point type	Secondary
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End point timeframe:

Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	66		
Units: percentage of participants				
number (confidence interval 95%)	5.9 (0.72 to 19.68)	19.7 (10.93 to 31.32)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Difference in proportions of Nusinersen minus Sham Procedure is based on exact unconditional confidence interval.	
Comparison groups	Sham procedure v Nusinersen
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
Parameter estimate	Difference in Proportions
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.64
upper limit	34.17

Notes:

[6] - Efficacy Set: All participants with a Day 456 Visit and all participants with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the date for the final analysis. Based on imputed data where there was missing data.

## Secondary: Number of New Motor Milestones Achieved per Participant

End point title	Number of New Motor Milestones Achieved per Participant
End point description:	
New motor milestones are defined as sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone.	
End point type	Secondary
End point timeframe:	
Month 15	

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	66		
Units: milestones achieved				
arithmetic mean (standard deviation)	-0.2 (± 0.54)	0.2 (± 0.51)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description: Based on ANCOVA with treatment as a fixed effect and adjustment for each participant's age at screening and number of milestones at baseline.	
Comparison groups	Sham procedure v Nusinersen
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority <sup>[7]</sup>
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.7

Notes:

[7] - Efficacy Set: All participants with a Day 456 Visit and all participants with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the date for the final analysis. Based on imputed data where there was missing data.

## Secondary: Change from Baseline in Revised Upper Limb Module (RULM) Test

End point title	Change from Baseline in Revised Upper Limb Module (RULM) Test
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End point description:

The RULM Test is used in patients with SMA to assess upper limb functional ability items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container). The RULM test has a total of 20 items with an entry item that serves as functional class identification and does not contribute to the total score. The remaining 19 scorable items reflect different functional domains and are graded on a 3-point system with a score of 0 (unable), 1 (able, with modification), and a maximum of 2 (able, no difficulty). There is only 1 item (item I) that is scored as a can/cannot score, with 1 as the highest score. Scorable items are summed for a total score range of 0-37, with higher scores increased great upper limb function. A positive change from Baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline and Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	84		
Units: scores on a scale				
least squares mean (confidence interval 95%)	0.5 (-0.6 to 1.6)	4.2 (3.4 to 5)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
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**Statistical analysis description:**

From multiple imputation procedure, based on ANCOVA with treatment as a fixed effect and adjustment for each participant's age at screening and derived total score at baseline.

Comparison groups	Sham procedure v Nusinersen
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	5

**Secondary: Percentage of Participants that Achieved Standing Alone**

End point title	Percentage of Participants that Achieved Standing Alone
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**End point description:**

If the participant was unable to achieve standing alone at Baseline but could achieve this at Month 15 then they were considered a responder. If they could not achieve this or if a participant terminated the study prior to the 15-month assessment due to treatment failure or death, then any imputed value was ignored and the participant was considered as a non-responder.

End point type	Secondary
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**End point timeframe:**

Month 15

<b>End point values</b>	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	66		
Units: percentage of participants				
number (confidence interval 95%)	2.9 (0.07 to 15.33)	1.5 (0.04 to 8.16)		

**Statistical analyses**

<b>Statistical analysis title</b>	Statistical Analysis 1
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**Statistical analysis description:**

Difference in proportions of Nusinersen minus Sham Procedure is based on exact unconditional confidence interval.

Comparison groups	Sham procedure v Nusinersen
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Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority <sup>[8]</sup>
Parameter estimate	Difference in Proportions
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.84
upper limit	19.34

Notes:

[8] - Efficacy Set: All participants with a Day 456 Visit and all participants with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the date for the final analysis. Based on imputed data where there was missing data.

## Secondary: Percentage of Participants that Achieved Walking with Assistance

End point title	Percentage of Participants that Achieved Walking with Assistance
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End point description:

If the participant was unable to achieve walking with assistance at baseline but could achieve this at Month 15 then they were considered a responder. If they could not achieve this or if a participant terminated the study prior to the 15-month assessment due to treatment failure or death, then any imputed value was ignored and the participant was considered as a non-responder.

End point type	Secondary
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End point timeframe:

Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	66		
Units: percentage pf participants				
number (confidence interval 95%)	0 (0 to 10.28)	1.5 (0.04 to 8.16)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Difference in proportions of Nusinersen minus Sham Procedure is based on exact unconditional confidence interval.

Comparison groups	Sham procedure v Nusinersen
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority <sup>[9]</sup>
Parameter estimate	Difference in Proportions
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	22.1

Notes:

[9] - Efficacy Set: All participants with a Day 456 Visit and all participants with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the date for the final analysis. Based on imputed data where there was missing data.

## Secondary: Number of Participants that Experienced Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants that Experienced Adverse Events (AEs) and Serious Adverse Events (SAEs)
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End point description:

AEs: any sign, symptom, or diagnosis/disease that is unfavorable or unintended, that is new, or if pre-existing, worsens in participants administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. SAEs: an event that results in death; an event that, in the view of the investigator, places the participant at immediate risk of death (a life-threatening event); an outcome that results in a congenital anomaly/birth defect diagnosed in a child of a participant; an event that requires or prolongs inpatient hospitalization; an event that results in persistent or significant disability/incapacity. Any other medically important event that, in the opinion of the investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

End point type	Secondary
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End point timeframe:

Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	84		
Units: participants				
AEs	42	78		
SAEs	12	14		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Clinically Significant Vital Sign Abnormalities

End point title	Number of Participants with Clinically Significant Vital Sign Abnormalities
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End point description:

Vital signs assessed for clinical significance include resting blood pressure, pulse, respiratory rate, and temperature.

End point type	Secondary
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End point timeframe:

Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[10]</sup>	0 <sup>[11]</sup>		
Units: participants				

Notes:

[10] - New or worsening vital sign findings were reported as AEs and are presented in the AE/SAE section.

[11] - New or worsening vital sign findings were reported as AEs and are presented in the AE/SAE section.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Clinically Significant Weight Abnormalities

End point title	Number of Participants with Clinically Significant Weight Abnormalities
End point description:	Weight changes assessed for clinical significance include body weight (including weight for age), ulnar length, and height (including height for age).
End point type	Secondary
End point timeframe:	Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[12]</sup>	0 <sup>[13]</sup>		
Units: participants				

Notes:

[12] - New or worsening weight abnormalities were reported as AEs and are presented in the AE/SAE section.

[13] - New or worsening weight abnormalities were reported as AEs and are presented in the AE/SAE section.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Clinically Significant Neurological Examination Abnormalities

End point title	Number of Participants with Clinically Significant Neurological Examination Abnormalities
End point description:	Neurological changes assessed for clinical significance include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.
End point type	Secondary

End point timeframe:

Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[14]</sup>	0 <sup>[15]</sup>		
Units: participants				

Notes:

[14] - New or worsening neurological findings were reported as AEs and are presented in the AE/SAE section.

[15] - New or worsening neurological findings were reported as AEs and are presented in the AE/SAE section.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Clinically Significant Physical Examination Abnormalities

End point title	Number of Participants with Clinically Significant Physical Examination Abnormalities
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End point description:

Physical examination changes were assessed for clinical significance.

End point type	Secondary
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End point timeframe:

Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[16]</sup>	0 <sup>[17]</sup>		
Units: participants				

Notes:

[16] - New or worsening physical exam findings were reported as AEs and are in the AE/SAE section.

[17] - New or worsening physical exam findings were reported as AEs and are in the AE/SAE section.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Clinically Significant Laboratory Parameters

End point title	Number of Participants with Clinically Significant Laboratory Parameters
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End point description:

Laboratory parameter changes assessed for clinical significance include serum chemistry, hematology, coagulation and urinalysis.

End point type	Secondary
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End point timeframe:

Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[18]</sup>	0 <sup>[19]</sup>		
Units: participants				

Notes:

[18] - New or worsening laboratory parameter findings were reported as AEs and are in the AE/SAE section.

[19] - New or worsening laboratory parameter findings were reported as AEs and are in the AE/SAE section.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Abnormal, Clinically Relevant Post-Baseline Worsening in Electrocardiogram (ECG) in Results

End point title	Number of Participants with Abnormal, Clinically Relevant Post-Baseline Worsening in Electrocardiogram (ECG) in Results
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End point description:

The number of participants with abnormal, clinically relevant worsening, defined as participants with an ECG interpreted as abnormal and clinically relevant, with a comparison with Baseline value is reported.

End point type	Secondary
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End point timeframe:

Baseline through Month 15

End point values	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	84		
Units: participants	2	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Taking Any Concomitant Medication Related to Dosing Procedure or Sham Procedure

End point title	Number of Participants Taking Any Concomitant Medication Related to Dosing Procedure or Sham Procedure
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End point description:

Concomitant medications include prescription and over-the-counter medications administered to participants on or after the first day of study treatment.

End point type	Secondary
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End point timeframe:

Baseline through Month 15

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<b>End point values</b>	Sham procedure	Nusinersen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	84		
Units: participants	42	84		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of Informed Consent to the end of the Follow-up period (Month 15)

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	17.1
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### Reporting groups

Reporting group title	Nusinersen
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Reporting group description:

Nusinersen 12 mg solution via intrathecal (IT) injection on Days 1, 29, 85 and 274.

Reporting group title	Sham procedure
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Reporting group description:

Sham comparator on Days 1, 29, 85 and 274.

Serious adverse events	Nusinersen	Sham procedure	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 84 (16.67%)	12 / 42 (28.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 84 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 84 (2.38%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 84 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 84 (1.19%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	2 / 84 (2.38%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 84 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 84 (2.38%)	6 / 42 (14.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia adenoviral			
subjects affected / exposed	0 / 84 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 84 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	3 / 84 (3.57%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 84 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 84 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Nusinersen	Sham procedure	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 84 (89.29%)	42 / 42 (100.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 84 (28.57%)	3 / 42 (7.14%)	
occurrences (all)	30	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	36 / 84 (42.86%)	15 / 42 (35.71%)	
occurrences (all)	52	30	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 84 (5.95%)	4 / 42 (9.52%)	
occurrences (all)	5	6	
Diarrhoea			
subjects affected / exposed	8 / 84 (9.52%)	3 / 42 (7.14%)	
occurrences (all)	9	3	
Vomiting			

subjects affected / exposed occurrences (all)	24 / 84 (28.57%) 29	5 / 42 (11.90%) 5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 84 (25.00%)	9 / 42 (21.43%)	
occurrences (all)	37	16	
Epistaxis			
subjects affected / exposed	6 / 84 (7.14%)	0 / 42 (0.00%)	
occurrences (all)	6	0	
Rhinorrhoea			
subjects affected / exposed	6 / 84 (7.14%)	7 / 42 (16.67%)	
occurrences (all)	10	15	
Upper respiratory tract congestion			
subjects affected / exposed	5 / 84 (5.95%)	2 / 42 (4.76%)	
occurrences (all)	6	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 84 (4.76%)	4 / 42 (9.52%)	
occurrences (all)	4	5	
Back pain			
subjects affected / exposed	21 / 84 (25.00%)	0 / 42 (0.00%)	
occurrences (all)	24	0	
Joint contracture			
subjects affected / exposed	4 / 84 (4.76%)	7 / 42 (16.67%)	
occurrences (all)	4	8	
Pain in extremity			
subjects affected / exposed	4 / 84 (4.76%)	3 / 42 (7.14%)	
occurrences (all)	4	3	
Scoliosis			
subjects affected / exposed	3 / 84 (3.57%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 84 (8.33%)	4 / 42 (9.52%)	
occurrences (all)	8	6	
Conjunctivitis			

subjects affected / exposed	6 / 84 (7.14%)	2 / 42 (4.76%)
occurrences (all)	6	2
Ear infection		
subjects affected / exposed	7 / 84 (8.33%)	5 / 42 (11.90%)
occurrences (all)	10	6
Gastroenteritis		
subjects affected / exposed	9 / 84 (10.71%)	8 / 42 (19.05%)
occurrences (all)	11	10
Gastroenteritis viral		
subjects affected / exposed	8 / 84 (9.52%)	4 / 42 (9.52%)
occurrences (all)	10	7
Influenza		
subjects affected / exposed	8 / 84 (9.52%)	2 / 42 (4.76%)
occurrences (all)	8	4
Nasopharyngitis		
subjects affected / exposed	20 / 84 (23.81%)	15 / 42 (35.71%)
occurrences (all)	40	25
Otitis media		
subjects affected / exposed	5 / 84 (5.95%)	4 / 42 (9.52%)
occurrences (all)	5	4
Pharyngitis streptococcal		
subjects affected / exposed	4 / 84 (4.76%)	3 / 42 (7.14%)
occurrences (all)	4	3
Pneumonia		
subjects affected / exposed	4 / 84 (4.76%)	6 / 42 (14.29%)
occurrences (all)	6	9
Upper respiratory tract infection		
subjects affected / exposed	25 / 84 (29.76%)	19 / 42 (45.24%)
occurrences (all)	39	32

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2014	Revised the statistical methods used to perform the interim analysis, revised the statistical methods used to perform the interim analysis, clarified the intention to continue safety follow-up via scheduled study visits for subjects who discontinue treatment without withdrawal of consent, added the main findings from nonclinical studies with ISIS 396443, clarified that general and local anesthesia and sedation were allowed to be used for LP procedure, added the neurological examination and HFMSE as appendices.
30 June 2016	Clarified the interim analysis plan, including its timing, subset of the total study population to be included, endpoints, and analytical methods used, clarified disposition of study subjects under the scenario of a premature study termination based on the results of a positive interim analysis, added language to describe the potential changes to study conduct that may occur on the basis of a positive benefit-risk assessment of the results of the interim analysis, added a statement regarding unblinding of certain representatives of the Sponsor during the interim analysis, updated clinical experience information to match Investigator's Brochure, Version 6.0, January 2016, clarified adjustment of visit schedule for subjects who experience treatment delays as a result of illness, specific descriptions of the methodology for the efficacy endpoints was added, made minor changes to correct errors and improve clarity.

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.

After the positive interim analysis of the study, the decision was made in October 2016 to terminate the study early and participants were invited for end-of-study visits.

Notes: