



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | ISIS 396443-CS3B |
|-----------------------|------------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Biogen |
| Sponsor organisation address | 225 Binney Street, Cambridge, United States, United States, 02142 |
| Public contact | Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com |
| Scientific contact | Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001448-PIP01-13 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 November 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 November 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 122 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 122 |
| Number of subjects completed | 121 |

Pre-assignment subject non-completion reasons

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

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Control |

Arm description:

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

| | |
|---|-----------------|
| Arm type | Sham Comparator |
| No investigational medicinal product assigned in this arm | |

| | |
|------------------|------------|
| Arm title | Nusinersen |
|------------------|------------|

Arm description:

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

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

Dosage and administration details:

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

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject withdrew prior to receiving treatment and is accounted for in the Pre-Assignment Details.

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

Justification: Milestones describe the subjects' completion status.

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

Justification: Milestones describe the subjects' completion status.

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

Justification: Milestones describe the subjects' completion status.

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

Justification: Milestones describe the subjects' completion status.

Baseline characteristics

Reporting groups

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

| Reporting group values | Control | Nusinersen | Total |
|------------------------------------|---------|------------|-------|
| Number of subjects | 41 | 80 | 121 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|------------------|------------------|----|
| Age Continuous Units: days arithmetic mean standard deviation | 164.7 ± 48.54 | 147.2 ± 46.85 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 24 | 43 | 67 |
| Male | 17 | 37 | 54 |
| Age Continuous Age at First Dose Units: days arithmetic mean standard deviation | 180.5 ± 50.92 | 163.4 ± 49.57 | - |

End points

End points reporting groups

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

Primary: Percentage of Motor Milestones Responders

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

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

Statistical analyses

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

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

Primary: Time to Death or Permanent Ventilation

| | |
|---|--|
| End point title | Time to Death or Permanent Ventilation |
| End point description: | |
| Estimated proportion of participants who died or required permanent ventilation by a given study day, based on the Kaplan-Meier product-limit method. Time to death or permanent ventilation was defined as either tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event. This endpoint was adjudicated by a blinded, independent group of experienced clinicians, the Event Adjudication Committee (EAC), based on review of clinical study data and supporting information. Results are based on all available data. | |
| End point type | Primary |
| End point timeframe: | |
| Day 91, Day 182, Day 273, Day 364, Day 394 | |

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

Statistical analyses

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

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Control v Nusinersen |

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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

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

Secondary: Summary of Time to Death

| | |
|---|--------------------------|
| End point title | Summary of Time to Death |
| End point description: | |
| Estimated proportion of participants who died by given duration thresholds, based on the Kaplan-Meier product-limit method. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 91, Day 182, Day 273, Day 364, Day 394 | |

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

Statistical analyses

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

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

Secondary: Percentage of Participants Not Requiring Permanent Ventilation

| | |
|------------------------|--|
| End point title | Percentage of Participants Not Requiring Permanent Ventilation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Day 394 | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|--|
| End point title | Percentage of Compound Muscular Action Potential (CMAP) Responders |
| End point description: | |
| CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles. A participant was defined as a CMAP responder if the CMAP amplitude at the peroneal nerve was increasing to or maintained at ≥ 1 mV (comparing to the baseline) based on assessment at the later of the Day 183, Day 302, or Day 394 study visits. Results are based on all available data. | |
| End point type | Secondary |
| End point timeframe: | |
| assessed at the later of the Day 183, Day 302, or Day 394 study visits | |

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

Statistical analyses

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

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

| | |
|------------------------|---|
| End point title | Time to Death or Respiratory Intervention in the Subgroup of Participants Below the Study Median Disease Duration |
| End point description: | Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) among participants below the study median disease duration (13.1 weeks), by given duration thresholds, based on the Kaplan-Meier product-limit method. |
| End point type | Secondary |
| End point timeframe: | Day 91, Day 182, Day 273, Day 364, Day 394 |

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

Statistical analyses

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

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

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

| | |
|---|---|
| End point title | Time to Death or Respiratory Intervention in the Subgroup of Participants Above the Study Median Disease Duration |
| End point description: Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) among participants above the study median disease duration (13.1 weeks), by given duration thresholds, based on the Kaplan-Meier product-limit method. | |
| End point type | Secondary |
| End point timeframe: Day 91, Day 182, Day 273, Day 364, Day 394 | |

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

Statistical analyses

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

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

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

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

End point description:

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

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

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Screening through Day 394 (\pm 7 days) or early termination | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Number of Participants With AEs Corresponding to Changes in Hematology Values |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| up to Day 394 (\pm 7 days) or early termination | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to Day 394 (\pm 7 days) or early termination

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to Day 394 (\pm 7 days) or early termination

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

Notes:

[1] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to Day 394 (\pm 7 days) or early termination

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to Day 394 (\pm 7 days) or early termination

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening through Day 394 (\pm 7 days) or early termination

Adverse event reporting additional description:

Treatment-emergent events are presented.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Nusinersen |
|-----------------------|------------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 4 / 80 (5.00%) | 3 / 41 (7.32%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 2 / 41 (4.88%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site abscess | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 4 / 80 (5.00%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 6 / 41 (14.63%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Feeding disorder of infancy or early childhood | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 41 (4.88%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Feeding intolerance | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight gain poor | | | |

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported