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

## Summary

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

### Results information

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

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | ISIS 396443 - CS2 |

### Additional study identifiers

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

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 15 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 January 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 October 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 34 |
| Worldwide total number of subjects | 34 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 25 |

| | |
|---|---|
| Adolescents (12-17 years) | 9 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Nusinersen 3 mg |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Nusinersen 6 mg |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Nusinersen 9 mg |

Arm description:

9 mg nusinersen on Days 1 and 85, IT injection

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

Dosage and administration details:

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

"spinal anesthesia" needle and 5-mL syringe.

| **Arm title** | Nusinersen 12 mg |
|---|---|

Arm description:

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

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

Dosage and administration details:

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

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

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

## Baseline characteristics

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

| Reporting group values | Nusinersen 3 mg | Nusinersen 6 mg | Nusinersen 9 mg |
|---|---|---|---|
| Number of subjects | 8 | 8 | 9 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 5 | 5 | 8 |
| Adolescents (12-17 years) | 3 | 3 | 1 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 8.6 | 8.1 | 6 |
| standard deviation | ± 5.4 | ± 5.2 | ± 4 |
| Gender, Male/Female<br>Units: Participants | | | |
| Female | 4 | 3 | 4 |
| Male | 4 | 5 | 5 |

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

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

## End points

### End points reporting groups

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

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

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

End point description:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the study or use of the investigational drug product, whether or not the AE is considered related to the investigational drug product. An SAE is any AE that, in the view of either the Investigator or Sponsor, meets any of the following criteria: results in death; is life threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; results in congenital anomaly or birth defect; and is an important medical event in the judgment of the investigator. Drug-related is an event related or possibly related to study drug. Severity of AEs was assessed as mild, moderate, or severe.

| End point type | Primary |
|---|---|

End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented, per protocol.

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Pharmacokinetics: Maximal Observed Plasma Drug Concentration (Cmax)

| End point title | Plasma Pharmacokinetics: Maximal Observed Plasma Drug Concentration (Cmax) |
|---|---|

End point description:

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

End point timeframe:

Day 1 and Day 85

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Pharmacokinetics: Time to Reach Cmax in Plasma

| End point title | Plasma Pharmacokinetics: Time to Reach Cmax in Plasma |
|---|---|

End point description:

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

End point timeframe:

Day 1 and Day 85

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

Day 1 and Day 85

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

Day 1, Day 29, and Day 85

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

Notes:

[2] - 99999=below the limit of quantification (50 pg/mL). 999999=not applicable since 0 subjects analyzed.
[3] - 99999=below the limit of quantification (50 pg/mL).

### Statistical analyses

No statistical analyses for this end point

## Secondary: Urine Pharmacokinetics: Renal Clearance, Cohort 4

| End point title | Urine Pharmacokinetics: Renal Clearance, Cohort 4[4] |
|---|---|

End point description:

Renal clearance of nusinersen for participants was assessed in the 12 mg reporting group only, per protocol.

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

End point timeframe:

Day 1 and Day 85

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Nusinersen 3 mg |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Nusinersen 9 mg |

Reporting group description:

9 mg nusinersen on Days 1 and 85, IT injection

| | |
|---|---|
| Reporting group title | Nusinersen 12 mg |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Nusinersen 6 mg |

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported