



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ISIS 396443-CS4 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|-----------------------------------------------------------------------------------|
| Sponsor organisation name | Biogen |
| Sponsor organisation address | 225 Binney Street, Cambridge, United States, 02142 |
| Public contact | Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com |
| Scientific contact | Biogen Study Medical Director, Biogen, +1 866-633-4636, clinicaltrials@biogen.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001448-PIP13-02 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 February 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 February 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 February 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| 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) | 126 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sham procedure |

Arm description:

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

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

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

Arm description:

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

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

Dosage and administration details:

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

| Number of subjects in period 1 | Sham procedure | Nusinersen |
|--------------------------------|----------------|-------------------|
| Started | 42 | 84 |
| Completed Treatment | 42 | 83 ^[1] |
| Completed | 42 | 84 |

Notes:

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

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

Baseline characteristics

Reporting groups

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

| Reporting group values | Sham procedure | Nusinersen | Total |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|------------|-------|
| Number of subjects | 42 | 84 | 126 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 42 | 84 | 126 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 3.4 | 3.8 | - |
| standard deviation | ± 1.61 | ± 1.63 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 21 | 46 | 67 |
| Male | 21 | 38 | 59 |
| Study Specific Characteristic Hammersmith Functional Motor Scale - Expanded (HFMSE) Score | | | |
| The HFMSE consists of 33 scored activities used to assess motor function in children with SMA. Participants were asked to do a specific activity (such as rolling) and they were then graded on the quality and execution of that movement on a scale of 0=being unable, 1=performed with some compensation, and 2=unaided. The overall score is the sum of the scores for all activities with a maximum achievable score of 66. Higher scores indicate increased motor function. | | | |
| Units: scores on a scale | | | |
| arithmetic mean | 19.9 | 22.4 | - |
| standard deviation | ± 7.23 | ± 8.33 | - |

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

Notes:

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

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

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

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

End point description:

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

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

End point timeframe:

Baseline and Month 15

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

Statistical analyses

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

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

Notes:

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

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

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

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

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

| | |
|-----------------|------------------------------------------------------------------------------|
| End point title | Percentage of Participants that Achieved any New Motor Milestone at Month 15 |
|-----------------|------------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Month 15

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

Statistical analyses

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

Notes:

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

Secondary: Number of New Motor Milestones Achieved per Participant

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

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

Statistical analyses

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

Notes:

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

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

| | |
|-----------------|---------------------------------------------------------------|
| End point title | Change from Baseline in Revised Upper Limb Module (RULM) Test |
|-----------------|---------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Baseline and Month 15

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

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Secondary: Percentage of Participants that Achieved Standing Alone

| | |
|-----------------|---------------------------------------------------------|
| End point title | Percentage of Participants that Achieved Standing Alone |
|-----------------|---------------------------------------------------------|

End point description:

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

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

End point timeframe:

Month 15

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

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

| | |
|-------------------|-----------------------------|
| Comparison groups | Sham procedure v Nusinersen |
|-------------------|-----------------------------|

| | |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| Parameter estimate | Difference in Proportions |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.84 |
| upper limit | 19.34 |

Notes:

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

Secondary: Percentage of Participants that Achieved Walking with Assistance

| | |
|-----------------|------------------------------------------------------------------|
| End point title | Percentage of Participants that Achieved Walking with Assistance |
|-----------------|------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Month 15

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline through Month 15

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Vital Sign Abnormalities

| | |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Significant Vital Sign Abnormalities |
|-----------------|-----------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Baseline through Month 15

| End point values | Sham procedure | Nusinersen | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: participants | | | | |

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Weight Abnormalities

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

| End point values | Sham procedure | Nusinersen | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: participants | | | | |

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Neurological Examination Abnormalities

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

End point timeframe:

Baseline through Month 15

| End point values | Sham procedure | Nusinersen | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | | |
| Units: participants | | | | |

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Physical Examination Abnormalities

| | |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Significant Physical Examination Abnormalities |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

Physical examination changes were assessed for clinical significance.

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

End point timeframe:

Baseline through Month 15

| End point values | Sham procedure | Nusinersen | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: participants | | | | |

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Laboratory Parameters

| | |
|-----------------|--------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Significant Laboratory Parameters |
|-----------------|--------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

Baseline through Month 15

| End point values | Sham procedure | Nusinersen | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | | |
| Units: participants | | | | |

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline through Month 15

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline through Month 15

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

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

| | |
|-----------------------|----------------|
| Reporting group title | Sham procedure |
|-----------------------|----------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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

Notes: