



## Clinical trial results: Escalating Dose and Randomized, Controlled Study of Nusinersen (BIB058) in Participants With Spinal Muscular Atrophy Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2019-002663-10                   |
| Trial protocol           | LV IE HU PL ES GB DE FR GR IT NL |
| Global end of trial date | 30 May 2024                      |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 13 December 2024 |
| First version publication date | 13 December 2024 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 232SM203 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04089566 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 30 May 2024 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 30 May 2024 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study are to examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with spinal muscular atrophy (SMA), as measured by change in Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score (Part B); to examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA (Parts A and C).

Protection of trial subjects:

Written informed consent was obtained from each subject's parent or legal guardian prior to evaluations being performed for eligibility. Adequate time to review the information in the informed consent and ask questions concerning all portions of the conduct of the study was provided. Through the informed consent process, awareness of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken was made. 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                          | 26 March 2020 |
| 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: 23     |
| Country: Number of subjects enrolled | Japan: 6              |
| Country: Number of subjects enrolled | Germany: 4            |
| Country: Number of subjects enrolled | Italy: 4              |
| Country: Number of subjects enrolled | Spain: 19             |
| Country: Number of subjects enrolled | Canada: 2             |
| Country: Number of subjects enrolled | Taiwan: 9             |
| Country: Number of subjects enrolled | Estonia: 1            |
| Country: Number of subjects enrolled | Mexico: 15            |
| Country: Number of subjects enrolled | Saudi Arabia: 15      |
| Country: Number of subjects enrolled | China: 11             |
| Country: Number of subjects enrolled | Chile: 7              |
| Country: Number of subjects enrolled | Brazil: 10            |
| Country: Number of subjects enrolled | Poland: 4             |
| Country: Number of subjects enrolled | Russian Federation: 8 |

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Lebanon: 3  |
| Country: Number of subjects enrolled | Colombia: 2 |
| Country: Number of subjects enrolled | Hungary: 2  |
| Worldwide total number of subjects   | 145         |
| EEA total number of subjects         | 34          |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 4  |
| Infants and toddlers (28 days-23 months)  | 71 |
| Children (2-11 years)                     | 39 |
| Adolescents (12-17 years)                 | 7  |
| Adults (18-64 years)                      | 23 |
| From 65 to 84 years                       | 1  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part at the investigative sites in the United States, Brazil, Canada, Chile, China, Colombia, Estonia, Germany, Hungary, Italy, Japan, Lebanon, Mexico, Poland, Russia, Saudi Arabia, Spain, and Taiwan from 26 March 2020 to 30 May 2024.

### Pre-assignment

Screening details:

A total of 145 participants diagnosed with spinal muscular atrophy (SMA) were enrolled in the 3-parts (Parts A, B, and C). Of which, 117 of participants completed the study.

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes                                      |
| <b>Arm title</b>             | Part A: 28/28 Milligrams (mg) Nusinersen |

Arm description:

Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.

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

Dosage and administration details:

Administered as specified in the treatment arm.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen |
|------------------|--|

Arm description:

Participants with infantile-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

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

Dosage and administration details:

Administered as specified in the treatment arm.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
|------------------|--|

Arm description:

Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |  |
|---|--|
| Investigational medicinal product name          | Nusinersen                                   |
| Investigational medicinal product code          | BIIB058                                      |
| Other name                                      |  |
| Pharmaceutical forms                            | Solution for injection                       |
| Routes of administration                        | Intrathecal use                              |
| Dosage and administration details:              |  |
| Administered as specified in the treatment arm. |  |
| <b>Arm title</b>                                | Part B: Later-Onset SMA: 12/12 mg Nusinersen |

Arm description:

Participants with later-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

|   |  |
|---|--|
| Arm type  | Experimental                                 |
| Investigational medicinal product name          | Nusinersen                                   |
| Investigational medicinal product code          | BIIB058                                      |
| Other name                                      |  |
| Pharmaceutical forms                            | Solution for injection                       |
| Routes of administration                        | Intrathecal use                              |
| Dosage and administration details:              |  |
| Administered as specified in the treatment arm. |  |
| <b>Arm title</b>                                | Part B: Later-Onset SMA: 50/28 mg Nusinersen |

Arm description:

Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

|   |                             |
|---|-----------------------------|
| Arm type  | Experimental                |
| Investigational medicinal product name          | Nusinersen                  |
| Investigational medicinal product code          | BIIB058                     |
| Other name                                      |                             |
| Pharmaceutical forms                            | Solution for injection      |
| Routes of administration                        | Intrathecal use             |
| Dosage and administration details:              |                             |
| Administered as specified in the treatment arm. |                             |
| <b>Arm title</b>                                | Part C: 50/28 mg Nusinersen |

Arm description:

Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.

|   |                        |
|---|------------------------|
| Arm type  | Experimental           |
| Investigational medicinal product name          | Nusinersen             |
| Investigational medicinal product code          | BIIB058                |
| Other name                                      |                        |
| Pharmaceutical forms                            | Solution for injection |
| Routes of administration                        | Intrathecal use        |
| Dosage and administration details:              |                        |
| Administered as specified in the treatment arm. |                        |

| Number of subjects in period 1   | Part A: 28/28 Milligrams (mg) Nusinersen | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
|----------------------------------|--|--|--|
| Started                          | 6  | 25   | 50   |
| Completed                        | 6  | 13   | 35   |
| Not completed                    | 0  | 12   | 15   |
| Adverse event, serious fatal     | -  | 6  | 10   |
| Withdrawal by Parent or Guardian | -  | 2  | 1  |
| Reason not Specified             | -  | 4  | 4  |

| Number of subjects in period 1   | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen | Part C: 50/28 mg Nusinersen |
|----------------------------------|--|--|-----------------------------|
| Started                          | 8  | 16   | 40                          |
| Completed                        | 7  | 16   | 40                          |
| Not completed                    | 1  | 0  | 0                           |
| Adverse event, serious fatal     | -  | -  | -                           |
| Withdrawal by Parent or Guardian | -  | -  | -                           |
| Reason not Specified             | 1  | -  | -                           |

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Part A: 28/28 Milligrams (mg) Nusinersen         |
| Reporting group description:   |  |
| Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.  |  |
| Reporting group title  | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen |
| Reporting group description:   |  |
| Participants with infantile-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.  |  |
| Reporting group title  | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
| Reporting group description:   |  |
| Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.  |  |
| Reporting group title  | Part B: Later-Onset SMA: 12/12 mg Nusinersen     |
| Reporting group description:   |  |
| Participants with later-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.  |  |
| Reporting group title  | Part B: Later-Onset SMA: 50/28 mg Nusinersen     |
| Reporting group description:   |  |
| Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.  |  |
| Reporting group title  | Part C: 50/28 mg Nusinersen                      |
| Reporting group description:   |  |
| Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241. |  |

| Reporting group values                           | Part A: 28/28 Milligrams (mg) Nusinersen | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
|--|--|--|--|
| Number of subjects                               | 6  | 25   | 50   |
| Age categorical                                  |  |  |  |
| Units: participants                              |  |  |  |
| In Utero   | 0  | 0  | 0  |
| Preterm newborn infants (gestational age<37 wks) | 0  | 0  | 0  |
| Newborns (0-27 days)                             | 0  | 1  | 3  |
| Infants and toddlers (28 days - 23 months)       | 0  | 24   | 47   |
| Children (2 - 11 years)                          | 5  | 0  | 0  |
| Adolescents (12 - 17 years)                      | 1  | 0  | 0  |
| Adults (18 - 64 years)                           | 0  | 0  | 0  |
| From 65 - 84 years                               | 0  | 0  | 0  |
| 85 years and over                                | 0  | 0  | 0  |
| Gender categorical                               |  |  |  |
| Units: participants                              |  |  |  |
| Male   | 5  | 14   | 26   |

|        |   |    |    |
|--------|---|----|----|
| Female | 1 | 11 | 24 |
|--------|---|----|----|

  

|   |   |    |    |
|---|---|----|----|
| Race  |   |    |    |
| Units: Subjects                                 |   |    |    |
| American Indian or Alaska Native                | 0 | 0  | 2  |
| Asian   | 2 | 4  | 10 |
| Black or African American                       | 0 | 0  | 0  |
| Native Hawaiian or other Pacific Islander       | 0 | 0  | 0  |
| White   | 4 | 17 | 29 |
| Not Reported Due to Confidentiality Regulations | 0 | 0  | 2  |
| Other   | 0 | 4  | 7  |
| Multiple  | 0 | 0  | 0  |
| Ethnicity                                       |   |    |    |
| Units: Subjects                                 |   |    |    |
| Hispanic or Latino                              | 1 | 10 | 18 |
| Not Hispanic or Latino                          | 5 | 13 | 30 |
| Not reported                                    | 0 | 2  | 2  |

| Reporting group values                              | Part B: Later-Onset<br>SMA: 12/12 mg<br>Nusinersen | Part B: Later-Onset<br>SMA: 50/28 mg<br>Nusinersen | Part C: 50/28 mg<br>Nusinersen |
|---|--|--|--------------------------------|
| Number of subjects                                  | 8  | 16   | 40                             |
| Age categorical                                     |  |  |                                |
| Units: participants                                 |  |  |                                |
| In Utero  | 0  | 0  | 0                              |
| Preterm newborn infants<br>(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)                             | 8  | 16   | 10                             |
| Adolescents (12 - 17 years)                         | 0  | 0  | 6                              |
| Adults (18 - 64 years)                              | 0  | 0  | 23                             |
| From 65 - 84 years                                  | 0  | 0  | 1                              |
| 85 years and over                                   | 0  | 0  | 0                              |
| Gender categorical                                  |  |  |                                |
| Units: participants                                 |  |  |                                |
| Male  | 2  | 2  | 25                             |
| Female  | 6  | 14   | 15                             |
| Race  |  |  |                                |
| Units: Subjects                                     |  |  |                                |
| American Indian or Alaska Native                    | 0  | 0  | 0                              |
| Asian   | 2  | 5  | 7                              |
| Black or African American                           | 0  | 1  | 0                              |
| Native Hawaiian or other Pacific Islander           | 0  | 0  | 0                              |
| White   | 3  | 8  | 32                             |
| Not Reported Due to Confidentiality Regulations     | 0  | 0  | 0                              |
| Other   | 3  | 2  | 1                              |
| Multiple  | 0  | 0  | 0                              |



|                        |   |    |    |
|------------------------|---|----|----|
| Ethnicity              |   |    |    |
| Units: Subjects        |   |    |    |
| Hispanic or Latino     | 2 | 6  | 5  |
| Not Hispanic or Latino | 6 | 10 | 35 |
| Not reported           | 0 | 0  | 0  |

|  |       |  |  |
|--|-------|--|--|
| <b>Reporting group values</b>                    | Total |  |  |
| Number of subjects                               | 145   |  |  |
| Age categorical                                  |       |  |  |
| Units: participants                              |       |  |  |
| In Utero   | 0     |  |  |
| Preterm newborn infants (gestational age<37 wks) | 0     |  |  |
| Newborns (0-27 days)                             | 4     |  |  |
| Infants and toddlers (28 days - 23 months)       | 71    |  |  |
| Children (2 - 11 years)                          | 39    |  |  |
| Adolescents (12 - 17 years)                      | 7     |  |  |
| Adults (18 - 64 years)                           | 23    |  |  |
| From 65 - 84 years                               | 1     |  |  |
| 85 years and over                                | 0     |  |  |
| Gender categorical                               |       |  |  |
| Units: participants                              |       |  |  |
| Male   | 74    |  |  |
| Female   | 71    |  |  |
| Race   |       |  |  |
| Units: Subjects                                  |       |  |  |
| American Indian or Alaska Native                 | 2     |  |  |
| Asian  | 30    |  |  |
| Black or African American                        | 1     |  |  |
| Native Hawaiian or other Pacific Islander        | 0     |  |  |
| White  | 93    |  |  |
| Not Reported Due to Confidentiality Regulations  | 2     |  |  |
| Other  | 17    |  |  |
| Multiple   | 0     |  |  |
| Ethnicity  |       |  |  |
| Units: Subjects                                  |       |  |  |
| Hispanic or Latino                               | 42    |  |  |
| Not Hispanic or Latino                           | 99    |  |  |
| Not reported                                     | 4     |  |  |

### Subject analysis sets

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | CS3B Matched Sham Control Group |
| Subject analysis set type  | Full analysis                   |

Subject analysis set description:

Historical data of participants who received sham treatment, IT, on Days 1, 15, 29, 64, 183, and 302 in the double-blind, phase 3 study CS3B (2013-004422-29), was used as control in the current study.

| <b>Reporting group values</b>                       | CS3B Matched Sham<br>Control Group |  |  |
|---|------------------------------------|--|--|
| Number of subjects                                  | 20                                 |  |  |
| Age categorical<br>Units: participants              |                                    |  |  |
| In Utero  | 0                                  |  |  |
| Preterm newborn infants<br>(gestational age<37 wks) | 0                                  |  |  |
| Newborns (0-27 days)                                | 0                                  |  |  |
| Infants and toddlers (28 days - 23<br>months)       | 0                                  |  |  |
| Children (2 - 11 years)                             | 0                                  |  |  |
| Adolescents (12 - 17 years)                         | 0                                  |  |  |
| Adults (18 - 64 years)                              | 0                                  |  |  |
| From 65 - 84 years                                  | 0                                  |  |  |
| 85 years and over                                   | 0                                  |  |  |
| Gender categorical<br>Units: participants           |                                    |  |  |
| Male  | 0                                  |  |  |
| Female  | 0                                  |  |  |
| Race<br>Units: Subjects                             |                                    |  |  |
| American Indian or Alaska Native                    | 0                                  |  |  |
| Asian   | 0                                  |  |  |
| Black or African American                           | 0                                  |  |  |
| Native Hawaiian or other Pacific<br>Islander        | 0                                  |  |  |
| White   | 0                                  |  |  |
| Not Reported Due to Confidentiality<br>Regulations  | 0                                  |  |  |
| Other   | 0                                  |  |  |
| Multiple  | 0                                  |  |  |
| Ethnicity<br>Units: Subjects                        |                                    |  |  |
| Hispanic or Latino                                  | 0                                  |  |  |
| Not Hispanic or Latino                              | 0                                  |  |  |
| Not reported  | 0                                  |  |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Part A: 28/28 Milligrams (mg) Nusinersen         |
| Reporting group description:<br>Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.  |  |
| Reporting group title  | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen |
| Reporting group description:<br>Participants with infantile-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.  |  |
| Reporting group title  | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
| Reporting group description:<br>Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.  |  |
| Reporting group title  | Part B: Later-Onset SMA: 12/12 mg Nusinersen     |
| Reporting group description:<br>Participants with later-onset SMA in the control group received 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.  |  |
| Reporting group title  | Part B: Later-Onset SMA: 50/28 mg Nusinersen     |
| Reporting group description:<br>Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.  |  |
| Reporting group title  | Part C: 50/28 mg Nusinersen                      |
| Reporting group description:<br>Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241. |  |
| Subject analysis set title   | CS3B Matched Sham Control Group                  |
| Subject analysis set type  | Full analysis                                    |
| Subject analysis set description:<br>Historical data of participants who received sham treatment, IT, on Days 1, 15, 29, 64, 183, and 302 in the double-blind, phase 3 study CS3B (2013-004422-29), was used as control in the current study.  |  |

### Primary: Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

|   |  |
|---|--|
| End point title   | Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group <sup>[1]</sup> |
| End point description:<br>The CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. It included 16 items (capturing neck, trunk, and proximal and distal limb strength), nine of which were scored 0, 1, 2, 3, or 4, five were scored as 0, 2, or 4, one was scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4 with greater scores indicating greater muscle strength. Total score ranged from 0 (worst possible score) and 64 (best possible score). The change from baseline to Day 183 in the CHOP-INTEND total score was compared to CS3B study (2013-004422-29) sham control group using the joint-rank methodology to account for mortality. As stated in protocol a matched sham set was defined for the analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set. |  |
| End point type  | Primary  |

End point timeframe:

Baseline, Day 183

Notes:

[1] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen | CS3B Matched<br>Sham Control<br>Group |  |  |
|--|---|---------------------------------------|--|--|
| Subject group type                           | Reporting group   | Subject analysis set                  |  |  |
| Number of subjects analysed                  | 50  | 20                                    |  |  |
| Units: score on scale                        |   |                                       |  |  |
| least squares mean (confidence interval 95%) | 42.9 (38.7 to 47.2)                                       | 16.9 (10.1 to 23.7)                   |  |  |

## Statistical analyses

| Statistical analysis title              | Change From Baseline in CHOP-INTEND Total Score                                    |
|---|--|
| Comparison groups                       | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen v CS3B Matched Sham Control Group |
| Number of subjects included in analysis | 70   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 [2]   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least square (LS) mean difference  |
| Point estimate                          | 26.06  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 17.941   |
| upper limit                             | 34.172   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 4.141  |

Notes:

[2] - The Analysis of Covariance (ANCOVA) model used rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

## Primary: Parts A and C: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (TESAEs)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (TESAEs) <sup>[3][4]</sup> |
|-----------------|--|

End point description:

An adverse event (AE): any unfavorable & unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with use of an investigational product, whether or not related to investigational product. SAE: any untoward medical occurrence that at any dose resulted in death, in view of Investigator, placed participant at immediate risk of death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a birth defect. AE and SAEs were regarded as treatment-emergent if it was present prior to receiving first dose of nusinersen in current study and subsequently worsened in severity or was not present prior to receiving first dose of nusinersen and subsequently

appeared Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study.

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

End point timeframe:

Part A: From the first dose of the study drug up to Day 389, Part C: From the first dose of the study drug up to Day 361

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[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: Parts A and C arms were planned to be analysed for this end point.

|                             |   |                                |  |  |
|-----------------------------|---|--------------------------------|--|--|
| <b>End point values</b>     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
| Subject group type          | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed | 6   | 40                             |  |  |
| Units: participants         |   |                                |  |  |
| TEAEs                       | 4   | 37                             |  |  |
| TESAEs                      | 1   | 6                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters) <sup>[5][6]</sup> |
|-----------------|--|

End point description:

Blood chemistry parameters included protein, albumin, creatinine, blood urea nitrogen, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, and creatine kinase. Parameters were flagged as low, normal/ high relative to normal range/ as unknown if no result was available, by Investigator. Here, shift to low indicates values that were normal, high/ unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. Categories with at least one participant with shift from baseline are reported. Part A: safety analysis set. Part C: ITT set. Safety and ITT set included all participants who received at least one dose of nusinersen. Number analyzed 'n' is number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[6] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                                     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|--|---|--------------------------------|--|--|
| Subject group type                                   | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed                          | 6   | 40                             |  |  |
| Units: participants                                  |   |                                |  |  |
| Alkaline Phosphatase Shift to High<br>(n=6,39)       | 1   | 2                              |  |  |
| Alanine Aminotransferase Shift to<br>High(n=6,34)    | 0   | 6                              |  |  |
| Aspartate Aminotransferase Shift to<br>High (n=6,37) | 0   | 8                              |  |  |
| Bicarbonate Shift to Low (n=2,31)                    | 1   | 6                              |  |  |
| Bicarbonate Shift to High (n=2,40)                   | 0   | 2                              |  |  |
| Bilirubin Shift to High (n=6,40)                     | 0   | 1                              |  |  |
| Indirect Bilirubin Shift to Low (n=4,26)             | 4   | 12                             |  |  |
| Indirect Bilirubin Shift to High (n=6,40)            | 0   | 1                              |  |  |
| Calcium Shift to High (n=6,39)                       | 0   | 1                              |  |  |
| Creatine Kinase Shift to Low (n=6,39)                | 0   | 0                              |  |  |
| Creatine Kinase Shift to High (n=3,22)               | 0   | 1                              |  |  |
| Chloride Shift to Low (n=6,40)                       | 0   | 1                              |  |  |
| Creatinine Shift to Low (n=1,2)                      | 0   | 1                              |  |  |
| Glucose Shift to Low (n=6,37)                        | 0   | 3                              |  |  |
| Glucose Shift to High (n=5,33)                       | 3   | 9                              |  |  |
| Potassium Shift to High (n=6,39)                     | 1   | 1                              |  |  |
| Phosphate Shift to High (n=5,36)                     | 2   | 10                             |  |  |
| Sodium Shift to High (n=6,40)                        | 0   | 1                              |  |  |
| Urea Nitrogen Shift to Low (n=6,39)                  | 0   | 1                              |  |  |
| Urea Nitrogen Shift to High (n=6,39)                 | 1   | 3                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Hematology Parameters)

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Hematology Parameters) <sup>[7][8]</sup> |
|-----------------|---|

End point description:

Hematology parameters included complete blood cell count, with differential and platelet count, and absolute neutrophil count. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Number analysed (n)' indicates the number of participants evaluable for the specified hematology parameter.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[8] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                             | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|--|---|--------------------------------|--|--|
| Subject group type                           | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed                  | 6   | 40                             |  |  |
| Units: participants                          |   |                                |  |  |
| Basophils Shift to High (n=3,37)             | 2   | 6                              |  |  |
| Basophils/Leukocytes Shift to High(n=2,35)   | 2   | 6                              |  |  |
| Eosinophils Shift to High(n=5,39)            | 1   | 3                              |  |  |
| Eosinophils/Leukocytes Shift to High(n=4,36) | 3   | 9                              |  |  |
| Hematocrit Shift to Low(n=5,40)              | 0   | 2                              |  |  |
| Hematocrit Shift to High(n=6,40)             | 1   | 0                              |  |  |
| Hemoglobin Shift to Low(n=6,40)              | 0   | 3                              |  |  |
| Lymphocytes Shift to High(n=5,39)            | 0   | 1                              |  |  |
| Lymphocytes/Leukocytes Shift to Low(n=6,39)  | 0   | 2                              |  |  |
| Lymphocytes/Leukocytes Shift to High(n=6,36) | 0   | 3                              |  |  |
| Monocytes Shift to Low(n=4,39)               | 1   | 4                              |  |  |
| Monocytes/Leukocytes Shift to Low(n=4,35)    | 3   | 2                              |  |  |
| Monocytes/Leukocytes Shift to High(n=6,40)   | 0   | 2                              |  |  |
| Neutrophils Shift to Low(n=6,35)             | 0   | 5                              |  |  |
| Neutrophils Shift to High(n=6,40)            | 0   | 2                              |  |  |
| Neutrophils/Leukocytes Shift to Low (n=5,38) | 1   | 4                              |  |  |
| Neutrophils/Leukocytes Shift to High(n=6,39) | 0   | 2                              |  |  |
| Platelets Shift to Low(n=6,39)               | 0   | 1                              |  |  |
| Platelets Shift to High(n=6,40)              | 0   | 1                              |  |  |
| Leukocytes Shift to Low(n=6,36)              | 0   | 3                              |  |  |
| Leukocytes Shift to High(n=6,40)             | 0   | 3                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Urinalysis Parameters)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Clinical Laboratory Parameters (Urinalysis Parameters) <sup>[9][10]</sup> |
|-----------------|--|

**End point description:**

Urinalysis included assessments of urine total protein, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts and crystals. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Number analysed (n)' indicates the number of participants evaluable for the specified urinalysis parameter.

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

**End point timeframe:**

Parts A and C: Baseline up to Day 302

**Notes:**

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

Justification: Only descriptive statistics were planned for this endpoint.

[10] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                        | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|---|--|-----------------------------|--|--|
| Subject group type                      | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed             | 6  | 40                          |  |  |
| Units: participants                     |  |                             |  |  |
| Specific Gravity Shift to High (n=5,40) | 2  | 1                           |  |  |
| pH Shift to High (n=6,40)               | 0  | 2                           |  |  |
| Protein High/positive (n=5,38)          | 4  | 9                           |  |  |
| Glucose High/positive (n=6,40)          | 0  | 2                           |  |  |
| Ketones High/positive (n=5,36)          | 1  | 8                           |  |  |
| Occult Blood High/positive (n=6,38)     | 2  | 4                           |  |  |
| RBC High/positive (n=4,12)              | 1  | 1                           |  |  |
| WBC High/positive (n=2,23)              | 0  | 2                           |  |  |
| Epithelial Cells High/positive (n=1,4)  | 0  | 4                           |  |  |
| Bacteria High/positive (n=1,2)          | 1  | 2                           |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Parts A and C: Number of Participants With Shifts From Baseline in Cerebrospinal Fluid (CSF) Parameters**

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Cerebrospinal Fluid (CSF) Parameters <sup>[11][12]</sup> |
|-----------------|---|

**End point description:**

CSF parameters included cell count, total protein, and glucose. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at



baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Number analysed (n)' indicates the number of participants evaluable for the specified urinalysis parameter.

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

End point timeframe:

Parts A: Baseline up to Day 269 Parts C: Baseline up to Day 241

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[12] - 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: Parts A and C arms were planned to be analysed for this end point.

|                                     |   |                                |  |  |
|-------------------------------------|---|--------------------------------|--|--|
| <b>End point values</b>             | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
| Subject group type                  | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed         | 6   | 40                             |  |  |
| Units: participants                 |   |                                |  |  |
| Glucose Shift to Low (n=5,38)       | 1   | 2                              |  |  |
| Glucose Shift to High (n=6,38)      | 0   | 2                              |  |  |
| Protein Shift to Low (n=6,39)       | 0   | 3                              |  |  |
| Protein Shift to High (n=6,37)      | 0   | 8                              |  |  |
| Erythrocytes Shift to High (n=5,34) | 2   | 8                              |  |  |
| Leukocytes Shift to High (n=5,36)   | 1   | 6                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Shifts From Baseline in Electrocardiograms (ECGs)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Electrocardiograms (ECGs) <sup>[13][14]</sup> |
|-----------------|--|

End point description:

The ECGs were assessed by the investigator to be normal, abnormal and abnormal AE. The number of participants with ECG shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) was assessed. Shift from baseline to worst post-baseline values were reported. The categories with at least one participant with shift from baseline in ECG are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[14] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                     | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|--------------------------------------|--|-----------------------------|--|--|
| Subject group type                   | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed          | 6  | 40                          |  |  |
| Units: participants                  |  |                             |  |  |
| Normal to Normal                     | 0  | 10                          |  |  |
| Normal to Abnormal, not AE           | 3  | 12                          |  |  |
| Abnormal, not AE to Abnormal, not AE | 3  | 17                          |  |  |
| Unknown to Abnormal, not AE          | 0  | 1                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Abnormalities in Vital Sign Parameters

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Number of Participants With Abnormalities in Vital Sign Parameters <sup>[15]</sup> <sup>[16]</sup> |
|-----------------|---|

End point description:

Vital sign assessment included temperature, pulse rate systolic blood pressure, diastolic blood pressure, and respiratory rate. As pre-specified in protocol, the criteria for determining potentially clinically relevant abnormalities in vital signs included: temperature < 36 and > 38 degrees Celsius (C), pulse rate < 60 and > 100 beats per minute (bpm), systolic blood pressure [< 90, > 140 and > 160 millimeters of mercury (mmHg)], diastolic blood pressure < 50, > 90 and > 100 mmHg and respiratory rate < 12 and > 20 breaths per minute. The categories with at least one participant with clinically relevant vital sign abnormalities are reported. Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[16] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values            | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|-----------------------------|--|-----------------------------|--|--|
| Subject group type          | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed | 6  | 40                          |  |  |
| Units: participants         |  |                             |  |  |
| Temperature <36.0 C         | 4  | 13                          |  |  |
| Pulse rate <60 bpm          | 1  | 14                          |  |  |

|                                   |   |    |  |  |
|-----------------------------------|---|----|--|--|
| Pulse rate >100 bpm               | 6 | 19 |  |  |
| Systolic blood pressure <90 mmHg  | 4 | 13 |  |  |
| Systolic blood pressure >140 mmHg | 0 | 3  |  |  |
| Diastolic blood pressure <50 mmHg | 3 | 10 |  |  |
| Diastolic blood pressure >90 mmHg | 1 | 7  |  |  |
| Respiratory rate <12 breaths/min  | 0 | 1  |  |  |
| Respiratory rate >20 breaths/min  | 6 | 27 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Change From Baseline in Growth Parameters (Ulnar Length)

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Change From Baseline in Growth Parameters (Ulnar Length) <sup>[17][18]</sup> |
|-----------------|---|

End point description:

As pre-specified in the protocol, ulnar length was measured for participants with later-onset SMA. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[18] - 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: Parts A and C arms were planned to be analysed for this end point.

|                                      |  |                             |  |  |
|--------------------------------------|--|-----------------------------|--|--|
| <b>End point values</b>              | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
| Subject group type                   | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed          | 6  | 27                          |  |  |
| Units: cm                            |  |                             |  |  |
| arithmetic mean (standard deviation) | 1.8 (± 1.43)                             | 0.0 (± 1.27)                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Part C: Change From Baseline in Growth Parameters (Arm Circumference)

|                 |   |
|-----------------|---|
| End point title | Part C: Change From Baseline in Growth Parameters (Arm Circumference) <sup>[19][20]</sup> |
|-----------------|---|

End point description:

As pre-specified in the protocol, arm circumference was measured for participants with infantile-onset

SMA. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Baseline, Day 302    |         |

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[20] - 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: Part C arm was planned to be analysed for this end point.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Part C: 50/28 mg Nusinersen |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 1                           |  |  |  |
| Units: cm                            |                             |  |  |  |
| arithmetic mean (standard deviation) | -1.0 (± 99999)              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Part C: Change From Baseline in Growth Parameters (Chest Circumference)

|                 |   |
|-----------------|---|
| End point title | Part C: Change From Baseline in Growth Parameters (Chest Circumference) <sup>[21][22]</sup> |
|-----------------|---|

End point description:

As pre-specified in protocol, chest circumference was measured for participants with infantile-onset SMA only. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Baseline, Day 302    |         |

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[22] - 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: Part C arm was planned to be analysed for this end point.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Part C: 50/28 mg Nusinersen |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 1                           |  |  |  |
| Units: cm                            |                             |  |  |  |
| arithmetic mean (standard deviation) | 2.5 (± 99999)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Part C: Change From Baseline in Growth Parameters (Head Circumference)

|                 |  |
|-----------------|--|
| End point title | Part C: Change From Baseline in Growth Parameters (Head Circumference) <sup>[23][24]</sup> |
|-----------------|--|

End point description:

As pre-specified in the protocol, head circumference was measured for participants with infantile-onset SMA only. ITT set included all participants who received at least one a dose of nusinersen in the current study. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[24] - 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: Part C arm was planned to be analysed for this end point.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| End point values                     | Part C: 50/28 mg Nusinersen |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 1                           |  |  |  |
| Units: cm                            |                             |  |  |  |
| arithmetic mean (standard deviation) | 2.0 (± 99999)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Parts A and C: Change From Baseline in Growth Parameters (Body Height)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Change From Baseline in Growth Parameters (Body Height) <sup>[25][26]</sup> |
|-----------------|--|

End point description:

Part A: safety analysis set. Part C: ITT set. Safety set and ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[26] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|--------------------------------------|---|--------------------------------|--|--|
| Subject group type                   | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed          | 2   | 32                             |  |  |
| Units: centimeters (cm)              |   |                                |  |  |
| arithmetic mean (standard deviation) | 7.2 (± 1.70)                                      | 0.8 (± 3.12)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Shifts from Baseline in Coagulation Parameters (Activated Partial Thromboplastin Time (aPTT))

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Number of Participants With Shifts from Baseline in Coagulation Parameters (Activated Partial Thromboplastin Time (aPTT)) <sup>[27][28]</sup> |
|-----------------|--|

End point description:

Activated partial thromboplastin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of aPTT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of aPTT at baseline to high values postbaseline.

Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure

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

End point timeframe:

Parts A and C: Baseline up to Day 269

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[28] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values            | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|-----------------------------|---|--------------------------------|--|--|
| Subject group type          | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed | 6   | 40                             |  |  |
| Units: participants         |   |                                |  |  |
| Shift to Low (n=6,40)       | 0   | 5                              |  |  |
| Shift to High (n=5,36)      | 0   | 1                              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (Prothrombin Time (PT))

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (Prothrombin Time (PT)) <sup>[29][30]</sup> |
|-----------------|---|

End point description:

Prothrombin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of PT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of PT at baseline to high values postbaseline. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure.

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

End point timeframe:

Parts A and C: Baseline up to Day 269

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[30] - 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: Parts A and C arms were planned to be analysed for this end point.

|                             |   |                                |  |  |
|-----------------------------|---|--------------------------------|--|--|
| <b>End point values</b>     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
| Subject group type          | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed | 6   | 40                             |  |  |
| Units: participants         |   |                                |  |  |
| Shift to Low (n=6,34)       | 0   | 0                              |  |  |
| Shift to High (n=6,32)      | 0   | 1                              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Parts A and C: Change From Baseline in Growth Parameters (Weight for Length Ratio)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Change From Baseline in Growth Parameters (Weight for Length Ratio) <sup>[31][32]</sup> |
|-----------------|--|

End point description:

Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[32] - 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: Parts A and C arms were planned to be analysed for this end point.

|                                      |  |                             |  |  |
|--------------------------------------|--|-----------------------------|--|--|
| <b>End point values</b>              | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
| Subject group type                   | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed          | 0 <sup>[33]</sup>                        | 0 <sup>[34]</sup>           |  |  |
| Units: ratio                         |  |                             |  |  |
| arithmetic mean (standard deviation) | ( )                                      | ( )                         |  |  |

Notes:

[33] - As the number of subjects analyzed was zero, mean and SD was not calculated.

[34] - As the number of subjects analyzed was zero, mean and SD was not calculated.

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Change From Baseline in Growth Parameters (Weight for Age Percentile)

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Change From Baseline in Growth Parameters (Weight for Age Percentile) <sup>[35][36]</sup> |
|-----------------|--|

End point description:

WHO child growth standards (WHO Child Growth Standards, 2006) was used to calculate the weight for age percentile in the infantile-onset participants. The 2000 CDC Growth Charts was used to calculate the weight for age percentile for later-onset participants. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[36] - 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: Parts A and C arms were planned to be analysed for this end point.



|                                      |  |                             |  |  |
|--------------------------------------|--|-----------------------------|--|--|
| <b>End point values</b>              | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
| Subject group type                   | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed          | 6  | 17                          |  |  |
| Units: percentile                    |  |                             |  |  |
| arithmetic mean (standard deviation) | 12.2 (± 12.84)                           | -2.7 (± 9.47)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Part C: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio)

|                 |   |
|-----------------|---|
| End point title | Part C: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio) <sup>[37][38]</sup> |
|-----------------|---|

End point description:

As pre-specified in the protocol, head to chest circumference ratio was assessed only for the participants with infantile-onset SMA. '99999' signifies that since one or no participant was evaluable, standard deviation (SD) was not estimated. ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[38] - 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: Part C arm was planned to be analysed for this end point.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Part C: 50/28 mg Nusinersen |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 1                           |  |  |  |
| Units: ratio                         |                             |  |  |  |
| arithmetic mean (standard deviation) | 0.0 (± 99999)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (International Normalized Ratio (INR))

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Number of Participants With Shifts From Baseline in Coagulation Parameters (International Normalized Ratio (INR)) <sup>[39][40]</sup> |
|-----------------|--|

---

**End point description:**

INR was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of INR at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of INR at baseline to high values postbaseline. The category with at least one participant with shift from baseline in INR ratio is reported. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure.

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

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**End point timeframe:**

Parts A and C: Baseline up to Day 269

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**Notes:**

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

Justification: Only descriptive statistics were planned for this endpoint.

[40] - 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: Parts A and C arms were planned to be analysed for this end point.

|                             |   |                                |  |  |
|-----------------------------|---|--------------------------------|--|--|
| <b>End point values</b>     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
| Subject group type          | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed | 6   | 40                             |  |  |
| Units: participants         |   |                                |  |  |
| Shift to Low (n=6,40)       | 0   | 3                              |  |  |
| Shift to High (n=6,39)      | 0   | 0                              |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Primary: Parts A and C: Change From Baseline in Urine Total Protein**

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|                 |  |
|-----------------|--|
| End point title | Parts A and C: Change From Baseline in Urine Total |
|-----------------|--|

---

**End point description:**

Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

---

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

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**End point timeframe:**

Parts A and C: Baseline, Day 302

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**Notes:**

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

Justification: Only descriptive statistics were planned for this endpoint.

[42] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|--------------------------------------|---|--------------------------------|--|--|
| Subject group type                   | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed          | 3   | 29                             |  |  |
| Units: grams per liter (g/L)         |   |                                |  |  |
| arithmetic mean (standard deviation) | 0.010 (±<br>0.1235)                               | -0.692 (±<br>3.7040)           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Parts A and C: Number of Participants With Neurological Examination Abnormalities Reported as AEs

|   |   |
|---|---|
| End point title   | Parts A and C: Number of Participants With Neurological Examination Abnormalities Reported as AEs <sup>[43]</sup> <sup>[44]</sup> |
| End point description:<br>Participants with abnormalities in neurological examinations recorded as AEs were reported. |   |
| End point type  | Primary   |
| End point timeframe:<br>Parts A and C: Baseline up to Day 302   |   |

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[44] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values            | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|-----------------------------|---|--------------------------------|--|--|
| Subject group type          | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed | 6   | 40                             |  |  |
| Units: participants         |   |                                |  |  |
| number (not applicable)     |   |                                |  |  |
| Vestibular Disorder         | 0   | 1                              |  |  |
| Asthenia                    | 0   | 1                              |  |  |
| Gait Disturbance            | 0   | 1                              |  |  |
| Balance Disorder            | 0   | 1                              |  |  |
| Disturbance in Attention    | 0   | 1                              |  |  |
| Paraesthesia                | 1   | 0                              |  |  |

## Statistical analyses

No statistical analyses for this end point

**Primary: Parts A and C: Percentage of Participants With a Postbaseline Corrected QT Interval Using Fridericia's Formula (QTcF) of > 500 milliseconds (msec) and an Increase From Baseline to any Postbaseline Timepoint in QTcF of > 60 msec**

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Percentage of Participants With a Postbaseline Corrected QT Interval Using Fridericia's Formula (QTcF) of > 500 milliseconds (msec) and an Increase From Baseline to any Postbaseline Timepoint in QTcF of > 60 msec <sup>[45]</sup> <sup>[46]</sup> |
|-----------------|---|

End point description:

As a part of safety assessment, QTcF was evaluated for determining the incidence of clinically relevant abnormalities. Post baseline QTcF of > 500 msec and maximum increase from baseline to post baseline QTcF > 60 msec was considered as a criteria for clinically relevant abnormality in ECG. Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[46] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                           | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|--|--|-----------------------------|--|--|
| Subject group type                         | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed                | 6  | 39                          |  |  |
| Units: percentage of participants          |  |                             |  |  |
| number (not applicable)                    |  |                             |  |  |
| Maximum Increase from Baseline QTcF>60msec | 0  | 0                           |  |  |
| Maximum Post Baseline QTcF > 500 msec      | 0  | 0                           |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Parts A and C: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements**

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements <sup>[47]</sup> <sup>[48]</sup> |
|-----------------|---|

End point description:

Part A: Safety set included all participants who received at least one dose of nusinersen. Part C:ITT set included all participants who received at least one a dose of nusinersen in the current study.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

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

Justification: Only descriptive statistics were planned for this endpoint.

[48] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                  | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|-----------------------------------|--|-----------------------------|--|--|
| Subject group type                | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed       | 6  | 40                          |  |  |
| Units: percentage of participants |  |                             |  |  |
| number (not applicable)           | 0  | 2.5                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Infantile-onset SMA: Percentage of Hammersmith Infant Neurological Examination (HINE) Section 2 Motor Milestone Responders for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Percentage of Hammersmith Infant Neurological Examination (HINE) Section 2 Motor Milestone Responders for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group <sup>[49]</sup> |
|-----------------|---|

End point description:

Section 2 of HINE was used to assess motor milestones of participants. It's composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, & walking. Motor milestone responder: a participant that demonstrated atleast a 2-point increase in ability to kick category or increase to maximal score on that category or a 1-point increase in motor milestones category of head control, rolling, sitting, crawling, standing, or walking & demonstrated improvement in more categories than worsening. Participants who died or withdrew from study were considered as non-responders. A matched sham set was defined per protocol for analysis of this outcome measure. Matched sham set comprised of sham control participants of CS3B study (2013-004422-29) identified by a matching algorithm& all of 50/28 mg participants in the ITT set.

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

End point timeframe:

Baseline up to Day 183

Notes:

[49] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | CS3B Matched Sham Control Group |  |  |
|---------------------------------|--|---------------------------------|--|--|
| Subject group type              | Reporting group                                  | Subject analysis set            |  |  |
| Number of subjects analysed     | 41   | 9                               |  |  |
| Units: percentage of responders |  |                                 |  |  |
| number (not applicable)         |  |                                 |  |  |

|   |    |   |  |  |
|---|----|---|--|--|
| Ability to kick: At least a 2-point increase  | 18 | 0 |  |  |
| Ability to kick: Achievement of touching toes | 8  | 0 |  |  |
| Head control: at least a 1-point increase     | 46 | 0 |  |  |
| Rolling: at least a 1-point increase          | 28 | 0 |  |  |
| Sitting: at least a 1-point increase          | 30 | 0 |  |  |
| Crawling: at least a 1-point increase         | 6  | 0 |  |  |
| Standing: at least a 1-point increase         | 14 | 0 |  |  |
| Walking: at least a 1-point increase          | 0  | 0 |  |  |
| Improvement in more categories than worsening | 58 | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of Neurofilament Light Chain (NF-L) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of Neurofilament Light Chain (NF-L) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group <sup>[50]</sup> |
|-----------------|---|

End point description:

The change from baseline in the plasma concentration of NF-L was compared to the study CS3B (2013-004422-29) matched sham control group. Joint rank methodology was used for the analysis to account for mortality. The change from baseline data was reported in terms of least square geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. As stated in protocol a matched sham set was defined for the analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set.

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

End point timeframe:

Baseline, Day 183

Notes:

[50] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | CS3B Matched Sham Control Group |  |  |
|--|--|---------------------------------|--|--|
| Subject group type                           | Reporting group                                  | Subject analysis set            |  |  |
| Number of subjects analysed                  | 50   | 20                              |  |  |
| Units: ratio                                 |  |                                 |  |  |
| least squares mean (confidence interval 95%) | 0.06 (0.05 to 0.06)                              | 0.70 (0.43 to 1.12)             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Change From Baseline in NF-L Plasma Concentration                                  |
| Comparison groups                       | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen v CS3B Matched Sham Control Group |
| Number of subjects included in analysis | 70   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 <sup>[51]</sup>   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS geometric mean ratio  |
| Point estimate                          | 0.08   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.05   |
| upper limit                             | 0.14   |

Notes:

[51] - ANCOVA model was used with treatment as a fixed effect and adjustment for each participant disease duration at screening, baseline log plasma NF-L and baseline CHOP INTEND total score.

## Secondary: Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group <sup>[52]</sup> |
|-----------------|---|

End point description:

Section 2 of the HINE was used to assess motor milestones of the participants. It's composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each category, 3 to 5 levels can be achieved. The total HINE section 2 motor milestones score was calculated as sum of each level & ranged from 0 to 26, higher score indicating improvement in motor milestones. A negative change from baseline indicates decline in motor milestones. Change from baseline in HINE section 2 motor milestones total score was compared to study CS3B (2013-004422-29) matched sham control group, was analysed using joint rank methodology. As stated in protocol a matched sham set was defined for analysis of this outcome measure. Matched sham set comprised of sham control participants of CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in ITT set.

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

End point timeframe:

Baseline, Day 183

Notes:

[52] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | CS3B Matched Sham Control Group |  |  |
|--|--|---------------------------------|--|--|
| Subject group type                           | Reporting group                                  | Subject analysis set            |  |  |
| Number of subjects analysed                  | 50   | 20                              |  |  |
| Units: score on scale                        |  |                                 |  |  |
| least squares mean (confidence interval 95%) | 43.1 (39.0 to 47.2)                              | 16.5 (9.9 to 23.0)              |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Change From Baseline in HINE Section Total Score                                   |
| Comparison groups                       | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen v CS3B Matched Sham Control Group |
| Number of subjects included in analysis | 70   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 <sup>[53]</sup>   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Least squares mean difference  |
| Point estimate                          | 26.67  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 18.812   |
| upper limit                             | 34.526   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 4.009  |

Notes:

[53] - ANCOVA model was used, rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

## Secondary: Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Infantile-onset SMA: Change From Baseline in CHOP-INTEND Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[54]</sup> |
|-----------------|--|

End point description:

The CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. It included 16 items (capturing neck, trunk, and proximal and distal limb strength), nine of which were scored 0, 1, 2, 3, or 4, five were scored as 0, 2, or 4, one was scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4 with greater scores indicating greater muscle strength. Total scores ranged from 0 (worst possible score) and 64 (best possible score). The change from baseline to Day 302 in the CHOP-INTEND total score was analyzed using the joint-rank methodology to account for mortality. ITT set included all participants who were randomized and received at least one dose of nusinersen.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 302    |           |

Notes:

[54] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |  |  |
|--|--|--|--|--|
| Subject group type                           | Reporting group                                  | Reporting group                                  |  |  |
| Number of subjects analysed                  | 25   | 50   |  |  |
| Units: score on scale                        |  |  |  |  |
| least squares mean (confidence interval 95%) | 37.3 (29.1 to 45.5)                              | 38.3 (32.7 to 44.0)                              |  |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change From Baseline in CHOP INTEND Total Score   |
| Comparison groups                       | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
| Number of subjects included in analysis | 75  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.8484 <sup>[55]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Least squares mean difference   |
| Point estimate                          | 1   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -9.29   |
| upper limit                             | 11.299  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 5.251   |

Notes:

[55] - ANCOVA model used rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

## Secondary: Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Infantile-onset SMA: Change From Baseline in HINE Section 2 Motor Milestones Total Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[56]</sup> |
|-----------------|--|

End point description:

Section 2 of the HINE was used to assess motor milestones of the participants. It's composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each of these categories, participants can progress from complete absence of a motor ability (the lowest level in each category) through multiple milestones (2 to 4 levels in each category) to the highest level within the category. The total motor milestones score for HINE section was calculated as the sum of each level and ranged from 0 to a maximum score of 26, higher score indicating improvement in motor milestones. ITT set included all participants who were randomized and received at least one dose of nusinersen.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 302    |           |

Notes:

[56] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

|  |   |   |  |  |
|--|---|---|--|--|
| <b>End point values</b>                      | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
| Subject group type                           | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                  | 25  | 50  |  |  |
| Units: score on scale                        |   |   |  |  |
| least squares mean (confidence interval 95%) | 33.9 (26.9 to 41.0)                                       | 40.0 (35.1 to 44.9)                                       |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change From Baseline in HINE Section Total Score  |
| Comparison groups                       | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
| Number of subjects included in analysis | 75  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.1734 <sup>[57]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Least squares mean difference   |
| Point estimate                          | 6.12  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.693  |
| upper limit                             | 14.939  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 4.497   |

Notes:

[57] - ANCOVA model used rank score as response, treatment as fixed effect and disease duration at screening, baseline HINE 2, baseline CHOP INTEND total score as covariates. Rank score of baseline covariates was used in model.

## Secondary: Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Infantile-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[58]</sup> |
|-----------------|--|

End point description:

The change from baseline in plasma concentration of NF-L was analysed using the joint rank methodology to account for mortality. The change from baseline data was reported in terms of LS geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who were randomized and received at least one dose of nusinersen.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 64     |           |

Notes:

[58] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

|  |   |   |  |  |
|--|---|---|--|--|
| <b>End point values</b>                      | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
| Subject group type                           | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                  | 25  | 50  |  |  |
| Units: ratio                                 |   |   |  |  |
| least squares mean (confidence interval 95%) | 0.23 (0.16 to 0.32)                                       | 0.12 (0.09 to 0.15)                                       |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change From Baseline in NF-L Plasma Concentration   |
| Comparison groups                       | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
| Number of subjects included in analysis | 75  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.002 <sup>[59]</sup>   |
| Method                                  | ANCOVA  |
| Parameter estimate                      | LS geometric mean ratio   |
| Point estimate                          | 0.51  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.33  |
| upper limit                             | 0.78  |

Notes:

[59] - ANCOVA model was used with treatment as a fixed effect and adjustment for each participant disease duration at screening, baseline log plasma NF-L and baseline CHOP INTEND total score.

## Secondary: Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

|                 |  |
|-----------------|--|
| End point title | Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group <sup>[60]</sup> |
|-----------------|--|

End point description:

Permanent ventilation was defined as tracheostomy or  $\geq 16$  hours of ventilation/day continuously for > 21 days in absence of an acute reversible event. An independent endpoint adjudication committee (EAC) determined date at which a participant was considered to have met protocol-specified criteria of an acute reversible event. Only events that were adjudicated by the EAC as meeting the criteria for permanent ventilation or death were included in analysis. As stated in protocol a matched sham set was defined for analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set. '99999' signifies that median and upper range of 95% confidence interval (CI) were not estimable due to low number events of permanent ventilation or death.

|                         |           |
|-------------------------|-----------|
| End point type          | Secondary |
| End point timeframe:    |           |
| Screening up to Day 399 |           |

Notes:

[60] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                 | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen | CS3B Matched<br>Sham Control<br>Group |  |  |
|----------------------------------|---|---------------------------------------|--|--|
| Subject group type               | Reporting group   | Subject analysis set                  |  |  |
| Number of subjects analysed      | 50  | 20                                    |  |  |
| Units: weeks                     |   |                                       |  |  |
| median (confidence interval 95%) | 99999 (39.86<br>to 99999)                                 | 19.1 (10.00 to<br>31.29)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group

|                 |  |
|-----------------|--|
| End point title | Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus CS3B Matched Sham Control Group <sup>[61]</sup> |
|-----------------|--|

End point description:

Time to death was determined by an independent EAC. Time to death (overall survival) was compared to the study CS3B (2013-004422-29) matched sham control group. As stated in protocol a matched sham set was defined for the analysis of this outcome measure. Matched sham set comprised of sham control participants of the CS3B study (2013-004422-29) identified by a matching algorithm and all of 50/28 mg participants in the ITT set. '99999' signifies that median and 95% CI were not estimable due to low number of events of death.

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

End point timeframe:

Screening up to Day 399

Notes:

[61] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                 | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen | CS3B Matched<br>Sham Control<br>Group |  |  |
|----------------------------------|---|---------------------------------------|--|--|
| Subject group type               | Reporting group   | Subject analysis set                  |  |  |
| Number of subjects analysed      | 50  | 20                                    |  |  |
| Units: weeks                     |   |                                       |  |  |
| median (confidence interval 95%) | 99999 (99999<br>to 99999)                                 | 33.6 (11.29 to<br>99999)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Later-onset SMA: Change From Baseline in Revised Upper Limb Module (RULM) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |   |
|-----------------|---|
| End point title | Part B Later-onset SMA: Change From Baseline in Revised |
|-----------------|---|

## End point description:

The RULM test was used in participants with later-onset 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 had a total of 20 items with an entry item that served as functional class identification and did not contribute to the total score. The remaining 19 scorable items reflected different functional domains and were graded on a 3-point system with a score of 0 (unable), 1 (able, with modification), and a maximum of 2 (able, no difficulty). Scorable items were summed for a total score range of 0-37, with higher scores indicating increased upper limb function. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable at the specified timepoint.

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

End point timeframe:

Baseline, Day 302

## Notes:

[62] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |  |  |
|--|--|--|--|--|
| Subject group type                           | Reporting group                              | Reporting group                              |  |  |
| Number of subjects analysed                  | 7  | 16   |  |  |
| Units: score on scale                        |  |  |  |  |
| least squares mean (confidence interval 95%) | 1.8 (-0.8 to 4.4)                            | 2.5 (0.7 to 4.2)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus 12/12mg Nusinersen**

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Time to Death or Permanent Ventilation for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[63]</sup> |
|-----------------|---|

## End point description:

Permanent ventilation was defined as tracheostomy or  $\geq 16$  hours of ventilation/day continuously for  $> 21$  days in the absence of an acute reversible event. An independent EAC determined the date at which a participant was considered to have met the protocol-specified criteria of an acute reversible event. Only events that were adjudicated by the EAC as meeting the protocol defined criteria for permanent ventilation or death was included in the analysis. ITT set included all participants who were randomized and received at least one dose of nusinersen. '99999' signifies that median or upper range of 95% confidence interval (CI) were not estimable due to low number events of permanent ventilation or death.

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

End point timeframe:

Screening up to Day 399

Notes:

[63] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                 | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed      | 25  | 50  |  |  |
| Units: weeks                     |   |   |  |  |
| median (confidence interval 95%) | 24.7 (14.43 to 99999)                                     | 99999 (39.86 to 99999)                                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Time to Death (Overall Survival) for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[64]</sup> |
|-----------------|---|

End point description:

Time to death was determined by an independent EAC. ITT set included all participants who were randomized and received at least one dose of nusinersen. '99999' signifies that median and 95% CI was not estimable due to low number events of death.

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

End point timeframe:

Screening up to Day 399

Notes:

[64] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                 | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed      | 25  | 50  |  |  |
| Units: weeks                     |   |   |  |  |
| median (confidence interval 95%) | 99999 (24.71 to 99999)                                    | 99999 (99999 to 99999)                                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Later-onset SMA: Change From Baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Later-onset SMA: Change From Baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) Score for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[65]</sup> |
|-----------------|--|

### End point description:

HFMSE scale was a tool used to assess motor function in children with later-onset SMA. The original 20 item Hammersmith Functional Motor Scale was expanded to include 13 additional adapted items from the Gross Motor Function Measure to improve sensitivity for the higher functioning ambulant population. Each item is scored 0 (unable), 1 (performs with modification or adaptation) or 2 (able) and the total score was calculated by summing the 33 items and ranged from 0 to 66 with higher scores indicating greater motor function. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

### End point timeframe:

Baseline, Day 302

### Notes:

[65] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |  |  |
|--|--|--|--|--|
| Subject group type                           | Reporting group                              | Reporting group                              |  |  |
| Number of subjects analysed                  | 7  | 15   |  |  |
| Units: score on scale                        |  |  |  |  |
| least squares mean (confidence interval 95%) | 2.6 (0.2 to 5.1)                             | 3.3 (1.5 to 5.0)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Later-onset SMA: Number of New World Health Organization (WHO) Motor Milestones for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |   |
|-----------------|---|
| End point title | Part B Later-onset SMA: Number of New World Health Organization (WHO) Motor Milestones for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[66]</sup> |
|-----------------|---|

### End point description:

The WHO motor milestones were a set of six milestones in motor development: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone and walking alone. The examiner recorded an overall rating of the participant's emotional state and then for each milestone one of the following four classifications: no (inability) - child tried but failed to perform the milestone, no (refusal) - child refused to perform despite being calm and alert, yes - child was able to perform the milestone, unable to test - could not be tested because of irritability, drowsiness or sickness. Mean of number of new milestones achieved was calculated and reported in this outcome measure. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this outcome measure.

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

### End point timeframe:

Baseline up to Day 302

Notes:

[66] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Later-Onset SMA:<br>12/12 mg<br>Nusinersen | Part B: Later-Onset SMA:<br>50/28 mg<br>Nusinersen |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                    | Reporting group                                    |  |  |
| Number of subjects analysed          | 7  | 16   |  |  |
| Units: motor milestones              |  |  |  |  |
| arithmetic mean (standard deviation) | 0.0 ( $\pm$ 0.00)                                  | 0.3 ( $\pm$ 1.00)                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Later-onset SMA: Change From Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Later-onset SMA: Change From Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[67]</sup> |
|-----------------|--|

End point description:

This assessment instrument was designed to quantify the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA. ACEND included domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance) and each domain comprises several items. The total score ranges from 0 to 100 with a higher score indicating decreased caregiver burden. A negative change from baseline indicates an increase in impact on caregiver. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for the specified parameter.

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

End point timeframe:

Baseline, Day 302

Notes:

[67] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                             | Part B: Later-Onset SMA:<br>12/12 mg<br>Nusinersen | Part B: Later-Onset SMA:<br>50/28 mg<br>Nusinersen |  |  |
|--|--|--|--|--|
| Subject group type                           | Reporting group                                    | Reporting group                                    |  |  |
| Number of subjects analysed                  | 7  | 16   |  |  |
| Units: score on scale                        |  |  |  |  |
| least squares mean (confidence interval 95%) |  |  |  |  |
| Feeding/Grooming/Dressing Total Score        | 7.9 (-4.8 to 20.6)                                 | 8.3 (-0.2 to 16.7)                                 |  |  |



|                          |                      |                    |  |  |
|--------------------------|----------------------|--------------------|--|--|
| Sitting/Play Total Score | 10.3 (0.6 to 20.0)   | 10.1 (3.6 to 16.6) |  |  |
| Transfers Total Score    | -0.0 (-10.9 to 10.9) | 9.9 (2.6 to 17.2)  |  |  |
| Mobility Total Score     | 6.9 (-7.2 to 20.9)   | 8.1 (-0.9 to 17.0) |  |  |
| Time Total Score         | -4.4 (-17.9 to 9.2)  | 11.9 (2.9 to 20.9) |  |  |
| Emotion Total Score      | 2.6 (-8.7 to 13.9)   | 2.5 (-5.0 to 10.0) |  |  |
| Finance Total Score      | -7.7 (-20.9 to 5.6)  | 7.8 (-0.7 to 31.7) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Later-onset SMA: Change From Baseline in Pediatric Quality of Life Inventory™ (PedsQL) for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Later-onset SMA: Change From Baseline in Pediatric Quality of Life Inventory™ (PedsQL) for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[68]</sup> |
|-----------------|--|

End point description:

PedsQL was used to measure health related quality of life (HRQOL) in children & adolescents. PedsQL generic core scale included assessment of physical functioning, emotional functioning, social functioning, and school functioning [PedsQL Inventory total score (PQLI)] and PedsQL Neuromuscular Module [Neuromuscular total score (PQLN)] measured HRQOL dimensions specific to with neuromuscular disorders, including SMA. Four dimensions were collected, each item scored on a 5-point ordinal scale (0=Never to 4=Almost Always). Items were reversed scored and were linearly transformed to a 0-100 scale. Total scale score was calculated as sum of all items over number of items answered on all scales. If more than 50% of items or more were missing, scale score was not computed. Higher scores indicated better health related quality of life. ITT set. Subjects analysed: number of participants evaluable for this endpoint. 'Number analysed (n)': number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[68] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                    | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |  |  |
|-------------------------------------|--|--|--|--|
| Subject group type                  | Reporting group                              | Reporting group                              |  |  |
| Number of subjects analysed         | 7  | 16   |  |  |
| Units: score on scale               |  |  |  |  |
| least squares mean (standard error) |  |  |  |  |
| PQLI-Total Score-Subject (n=4,12)   | -5.1 (± 4.73)                                | 3.8 (± 2.61)                                 |  |  |
| PQLI-Total Score-Parent (n=7,14)    | -9.6 (± 4.32)                                | -6.9 (± 2.96)                                |  |  |
| PQLN-Total Score-Subject (n=4,12)   | -4.8 (± 3.41)                                | 10.4 (± 1.91)                                |  |  |
| PQLN-Total Score-Parent (n=7,16)    | -6.4 (± 4.25)                                | -0.7 (± 2.81)                                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Later-onset SMA: Change From (Ratio to) Baseline in CSF Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |   |
|-----------------|---|
| End point title | Part B Later-onset SMA: Change From (Ratio to) Baseline in CSF Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[69]</sup> |
|-----------------|---|

#### End point description:

The change from baseline data was reported in terms of geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

#### End point timeframe:

Baseline, Day 279

#### Notes:

[69] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                         | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |  |  |
|--|--|--|--|--|
| Subject group type                       | Reporting group                              | Reporting group                              |  |  |
| Number of subjects analysed              | 7  | 16   |  |  |
| Units: pg/mL                             |  |  |  |  |
| geometric mean (confidence interval 95%) | 0.34 (0.23 to 0.50)                          | 0.34 (0.25 to 0.45)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Later-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen

|                 |  |
|-----------------|--|
| End point title | Part B Later-onset SMA: Change From (Ratio to) Baseline in Plasma Concentration of NF-L for 50/28mg Nusinersen Versus 12/12mg Nusinersen <sup>[70]</sup> |
|-----------------|--|

#### End point description:

The change from baseline data was reported in terms of geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who were randomized and received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline, Day 302  |           |
| Notes:   |           |
| [70] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.   |           |

|  |  |  |  |  |
|--|--|--|--|--|
| <b>End point values</b>                  | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |  |  |
| Subject group type                       | Reporting group                              | Reporting group                              |  |  |
| Number of subjects analysed              | 5  | 16   |  |  |
| Units: pg/mL                             |  |  |  |  |
| geometric mean (confidence interval 95%) | 0.28 (0.14 to 0.56)                          | 0.35 (0.24 to 0.51)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Number of Participants with TEAEs and TSEAEs

|   |  |
|---|--|
| End point title   | Part B: Number of Participants with TEAEs and TSEAEs <sup>[71]</sup> |
| End point description:  |  |
| AE was any unfavorable and unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An SAE was any untoward medical occurrence that at any dose resulted in death, in the view of the Investigator, placed the participant at immediate risk of death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a birth defect. AE was regarded as treatment-emergent if it was present prior to receiving the first dose of nusinersen in the current study and subsequently worsened in severity or was not present prior to receiving the first dose of nusinersen and subsequently appeared. Safety set included all participants who received at least one dose of nusinersen. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From the first dose of the study drug up to Day 399   |  |
| Notes:  |  |
| [71] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.   |  |

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
| Subject group type          | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed | 25   | 50   | 8  | 16   |
| Units: participants         |  |  |  |  |
| TEAEs                       | 22   | 45   | 7  | 14   |
| TSEAEs                      | 18   | 30   | 4  | 2  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Hematology Parameters)

|                 |  |
|-----------------|--|
| End point title | Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Hematology Parameters) <sup>[72]</sup> |
|-----------------|--|

End point description:

Hematology parameters included complete blood cell count, with differential and platelet count, and absolute neutrophil count. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified hematology parameter.

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

End point timeframe:

Baseline up to Day 302

Notes:

[72] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                                  | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|---|--|--|--|--|
| Subject group type                                | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed                       | 25   | 50   | 8  | 16   |
| Units: participants                               |  |  |  |  |
| Basophils Shift to Low (n=22,46,8,16)             | 0  | 2  | 0  | 0  |
| Basophils Shift to High (n=12,24,5,13)            | 7  | 17   | 4  | 8  |
| Basophils/Leukocytes Shift to High (n=11,21,4,9)  | 7  | 14   | 3  | 9  |
| Eosinophils Shift to Low (n=20,47,7,16)           | 0  | 7  | 1  | 0  |
| Eosinophils Shift to High (n=19,43,5,14)          | 6  | 15   | 0  | 1  |
| Eosinophil/Leukocyte Shift to Low (n=21,47,8,16)  | 0  | 4  | 0  | 0  |
| Eosinophil/Leukocyte Shift to High (n=15,28,5,12) | 8  | 12   | 1  | 5  |
| Hematocrit Shift to Low (n=20,43,8,16)            | 6  | 12   | 0  | 2  |
| Hematocrit Shift to High (n=22,47,8,15)           | 4  | 10   | 2  | 1  |
| Hemoglobin Shift to Low (n=22,45,7,14)            | 11   | 18   | 0  | 2  |
| Hemoglobin Shift to High (n=23,46,8,16)           | 3  | 2  | 0  | 0  |

|   |    |    |   |   |
|---|----|----|---|---|
| Lymphocytes Shift to Low (n=22,47,8,16)           | 3  | 6  | 1 | 1 |
| Lymphocytes Shift to High (n=19,41,7,14)          | 4  | 14 | 2 | 2 |
| Lymphocyte Atypical Shift to High(n=1,7,8,16)     | 0  | 5  | 0 | 0 |
| LymphocyteAtypical/LeukocyteShifttoHighn=1,7,8,16 | 0  | 4  | 0 | 0 |
| Lymphocyte/Leukocyte Shift to Low(n=22,45,8,16)   | 4  | 5  | 1 | 2 |
| Lymphocyte/Leukocyte Shift to High(n=20,43,7,16)  | 4  | 7  | 3 | 1 |
| Ery Mean Corpuscular Vol Shift to Lown=5,10,8,16  | 2  | 2  | 0 | 0 |
| Ery Mean Corpuscular Vol Shift to Highn=4,8,8,16  | 1  | 2  | 0 | 0 |
| Monocytes Shift to Low (n=22,46,7,15)             | 5  | 12 | 1 | 6 |
| Monocytes Shift to High (n=20,42,8,16)            | 5  | 13 | 2 | 2 |
| Monocytes/Leukocytes Shift to Low (n=21,44,6,14)  | 7  | 20 | 1 | 9 |
| Monocytes/Leukocytes Shift to High n=20,45,8,16   | 3  | 9  | 1 | 1 |
| Neutrophils Shift to Low (n=19,42,5,16)           | 5  | 9  | 1 | 2 |
| Neutrophils Shift to High (n=21,46,8,16)          | 11 | 13 | 1 | 1 |
| Neutrophils/Leukocytes Shift to Low n=19,39,7,16  | 4  | 13 | 4 | 0 |
| Neutrophils/Leukocytes ShifttoHigh n=21,45,7,16   | 6  | 6  | 1 | 1 |
| Platelets Shift to Low (n=23,47, 8,16)            | 1  | 2  | 0 | 1 |
| Platelets Shift to High (n=10,28,6,15)            | 4  | 14 | 1 | 4 |
| Erythrocytes Shift to Low (n=23,46,6,15)          | 4  | 10 | 0 | 0 |
| Erythrocytes Shift to High (n=22,47,8,13)         | 3  | 6  | 1 | 0 |
| Leukocytes Shift to Low (n=21,44,8,16)            | 4  | 13 | 2 | 0 |
| Leukocytes Shift to High (n=21,41,7,15)           | 10 | 15 | 1 | 2 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters)

|                 |   |
|-----------------|---|
| End point title | Part B: Number of Participants with Shifts from Baseline in Clinical Laboratory Parameters (Blood Chemistry Parameters) <sup>[73]</sup> |
|-----------------|---|

End point description:

Blood chemistry parameters included protein, albumin, creatinine, blood urea nitrogen, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, and creatine kinase. Parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. Categories with at least one participant with shift from baseline in these parameters are reported. Safety set included all participants who received at least a dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Baseline up to Day 302

Notes:

[73] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                                      | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|---|--|--|--|--|
| Subject group type                                    | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed                           | 25   | 50   | 8  | 16   |
| Units: participants                                   |  |  |  |  |
| Albumin Shift to Low (n=20,46,8,15)                   | 6  | 13   | 1  | 1  |
| Albumin Shift to High (n=23,50,8,16)                  | 1  | 2  | 0  | 0  |
| Alkaline Phosphatase Shift to Low (n=23,50,8,16)      | 0  | 3  | 0  | 0  |
| Alkaline Phosphatase Shift to High (n=23,50,8,16)     | 3  | 3  | 0  | 0  |
| Alanine Aminotransferase Shift to Low n=23,50,8,16    | 0  | 0  | 0  | 1  |
| Alanine Aminotransferase Shift to High n=14,39,6,15   | 4  | 14   | 0  | 3  |
| Aspartate Aminotransferase Shift to High n=21,45,7,16 | 5  | 9  | 0  | 1  |
| Bicarbonate Shift to Low (n=5,14,3,4)                 | 4  | 12   | 3  | 4  |
| Bicarbonate Shift to High (n=22,49,8,16)              | 1  | 1  | 0  | 0  |
| Direct Bilirubin Shift to Low (n=22,45,8,16)          | 1  | 0  | 0  | 0  |
| Bilirubin Shift to Low (n=21,49,8,16)                 | 2  | 2  | 0  | 1  |
| Bilirubin Shift to High (n=20,45,8,16)                | 1  | 1  | 0  | 0  |
| Indirect Bilirubin Shift to Low (n=22,46,2,4)         | 11   | 21   | 2  | 3  |
| Calcium Shift to Low (n=23,50,8,15)                   | 1  | 4  | 2  | 1  |
| Calcium Shift to High (n=19,45,8,15)                  | 8  | 17   | 0  | 0  |
| Creatine Kinase Shift to High (n=14,27,6,10)          | 6  | 12   | 3  | 3  |
| Chloride Shift to Low (n=23,50,8,16)                  | 3  | 3  | 0  | 1  |
| Chloride Shift to High (n=23,48,7,16)                 | 3  | 6  | 1  | 1  |
| Creatinine Shift to Low (n=2,5,0,1)                   | 2  | 5  | 0  | 1  |
| Creatinine Shift to High (n=23,50,8,16)               | 0  | 1  | 0  | 0  |
| Cystatin C Shift to Low (n=23,48,8,16)                | 2  | 0  | 1  | 1  |
| Cystatin C Shift to High (n=23,48,8,16)               | 2  | 1  | 0  | 0  |
| Gamma Glutamyl Transferase Shift to Low n=18,45,8,16  | 7  | 11   | 0  | 1  |
| Gamma Glutamyl Transferase Shift to High n=23,49,8,16 | 2  | 5  | 0  | 3  |
| Glucose Shift to Low (n=23,49,8,16)                   | 0  | 2  | 0  | 1  |
| Glucose Shift to High (n=20,44,7,15)                  | 6  | 17   | 2  | 6  |
| Potassium Shift to Low (n=23,50,8,16)                 | 1  | 2  | 0  | 1  |
| Potassium Shift to High (n=21,44,8,16)                | 5  | 15   | 3  | 4  |
| Lactate Dehydrogenase Shift to High (n=0,1,8,16)      | 0  | 1  | 0  | 0  |

|   |   |    |   |    |
|---|---|----|---|----|
| Magnesium Shift to High(n=3,5,8,16)       | 0 | 2  | 0 | 0  |
| Phosphate Shift to Low(n=23,50,8,16)      | 3 | 2  | 0 | 0  |
| Phosphate Shift to High(n=18,42,4,13)     | 5 | 16 | 2 | 10 |
| Protein Shift to Low(n=21,48,7,15)        | 7 | 9  | 1 | 2  |
| Protein Shift to High(n=23,47,8,16)       | 2 | 6  | 0 | 2  |
| Sodium Shift to Low(n=20,47,7,15)         | 3 | 15 | 2 | 3  |
| Sodium Shift to High(n=23,50,8,16)        | 0 | 0  | 0 | 1  |
| Urea Nitrogen Shift to Low(n=23,44,8,16)  | 1 | 3  | 2 | 1  |
| Urea Nitrogen Shift to High(n=23,50,8,15) | 0 | 0  | 2 | 1  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Number of Participants with Shifts from Baseline in Urinalysis

|                 |  |
|-----------------|--|
| End point title | Part B: Number of Participants with Shifts from Baseline in Urinalysis <sup>[74]</sup> |
|-----------------|--|

End point description:

Urinalysis included assessments of urine total protein, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, RBC, WBC, epithelial cells, bacteria, casts and crystals. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high, positive, abnormal or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, negative, absent, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Part A: safety analysis set. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Baseline up to Day 302

Notes:

[74] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                              | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|---|--|--|--|--|
| Subject group type                            | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed                   | 25   | 50   | 8  | 16   |
| Units: participants                           |  |  |  |  |
| Specific Gravity Shift to Low (n=20,47,8,16)  | 2  | 2  | 1  | 1  |
| Specific Gravity Shift to High (n=22,50,7,15) | 3  | 3  | 1  | 1  |
| pH Shift to Low (n=21,48,8,16)                | 2  | 1  | 0  | 1  |
| pH Shift to High (n=21,47,8,16)               | 5  | 8  | 1  | 1  |
| Protein High/positive (n=18,45,5,13)          | 12   | 27   | 3  | 9  |
| Glucose High/positive (n=21,46,8,16)          | 2  | 2  | 0  | 0  |
| Ketones High/positive (n=20,44,8,14)          | 5  | 16   | 4  | 4  |

|  |    |    |   |   |
|--|----|----|---|---|
| Occult Blood High/positive (n=16,43,7,14)  | 4  | 12 | 2 | 1 |
| RBC High/positive (n=13,26,7,12)           | 0  | 3  | 0 | 0 |
| WBC High/positive (n=15,25,6,10)           | 3  | 12 | 3 | 4 |
| Epithelial Cells High/positive (n=2,7,5,3) | 0  | 6  | 5 | 2 |
| Bacteria High/positive (n=10,18,2,8)       | 10 | 18 | 2 | 8 |
| Casts High/positive (n=3,3,8,16)           | 0  | 1  | 0 | 0 |
| Crystals High/positive (n=5,4,8,16)        | 2  | 1  | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants With Shifts From Baseline in CSF Parameters

|                 |  |
|-----------------|--|
| End point title | Part B: Number of Participants With Shifts From Baseline in CSF Parameters <sup>[75]</sup> |
|-----------------|--|

End point description:

CSF parameters included cell count, total protein, and glucose. These parameters were flagged as low, normal, or high relative to parameter's normal range or as unknown if no result was available, by the Investigator. Here, shift to low indicates values that were normal, high or unknown at baseline and shifted to low values postbaseline. Shift to high indicates values that were normal, low or unknown at baseline and shifted to high postbaseline. The categories with at least one participant with shift from baseline in these parameters are reported. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Baseline up to Day 302

Notes:

[75] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                          | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|---|--|--|--|--|
| Subject group type                        | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed               | 25   | 50   | 8  | 16   |
| Units: participants                       |  |  |  |  |
| Glucose Shift to Low (n=16,36,7,12)       | 4  | 3  | 1  | 0  |
| Glucose Shift to High (n=19,46,8,16)      | 0  | 1  | 0  | 0  |
| Protein Shift to Low (n=18,45,5,11)       | 2  | 6  | 0  | 4  |
| Protein Shift to High (n=12,25,8,15)      | 4  | 7  | 2  | 2  |
| Erythrocytes Shift to Low (n=18,47,8,15)  | 1  | 0  | 0  | 0  |
| Erythrocytes Shift to High (n=14,37,5,11) | 3  | 9  | 2  | 7  |
| Leukocytes Shift to Low (n=17,47,8,11)    | 1  | 2  | 0  | 1  |
| Leukocytes Shift to High (n=16,38,8,11)   | 1  | 5  | 0  | 4  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants With Shift From Baseline in ECGs

|                 |   |
|-----------------|---|
| End point title | Part B: Number of Participants With Shift From Baseline in ECGs <sup>[76]</sup> |
|-----------------|---|

End point description:

The ECGs were assessed by the investigator to be normal, abnormal and abnormal AE. The number of participants with ECG shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) was assessed. Shift from baseline to worst post-baseline values were reported. The categories with at least one participant with shift from baseline in ECG are reported. Safety set included all participants who received at least one dose of nusinersen.

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

End point timeframe:

Baseline up to Day 302

Notes:

[76] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed          | 25   | 50   | 8  | 16   |
| Units: participants                  |  |  |  |  |
| Normal to Normal                     | 2  | 7  | 0  | 0  |
| Normal to Abnormal, not AE           | 9  | 10   | 2  | 4  |
| Normal to Abnormal, AE               | 1  | 0  | 0  | 0  |
| Abnormal, not AE to Abnormal, not AE | 12   | 30   | 6  | 12   |
| Abnormal, not AE to Abnormal, AE     | 1  | 2  | 0  | 0  |
| Unknown to Abnormal, not AE          | 0  | 1  | 0  | 0  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants With Abnormalities in Vital Sign Parameters

|                 |  |
|-----------------|--|
| End point title | Part B: Number of Participants With Abnormalities in Vital Sign Parameters <sup>[77]</sup> |
|-----------------|--|

**End point description:**

Vital sign assessment included temperature, pulse rate systolic blood pressure, diastolic blood pressure, and respiratory rate. As pre-specified in protocol, the criteria for determining potentially clinically relevant abnormalities in vital signs included: temperature < 36 and > 38 degrees C, pulse rate < 60 and > 100 bpm, systolic blood pressure < 90, > 140 and > 160 mmHg, diastolic blood pressure < 50, > 90 and > 100 mmHg and respiratory rate < 12 and > 20 breaths per minute. The categories with at least one participant with clinically relevant vital sign abnormalities are reported. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Baseline up to Day 302

**Notes:**

[77] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                                 | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--|--|--|--|--|
| Subject group type                               | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed                      | 25   | 50   | 8  | 16   |
| Units: participants                              |  |  |  |  |
| Temperature <36.0 C (n=25,50,8,16)               | 6  | 23   | 3  | 7  |
| Temperature >38.0 C (n=25,50,8,16)               | 0  | 6  | 0  | 1  |
| Pulse Rate <60 bpm (n=25,50,8,16)                | 1  | 2  | 0  | 0  |
| Pulse Rate >100 bpm (n=25,50,8,16)               | 25   | 50   | 8  | 16   |
| Systolic Blood Pressure <90 mmHg (n=25,49,8,16)  | 24   | 47   | 7  | 10   |
| Systolic Blood Pressure >140 mmHg (n=25,49,8,16) | 3  | 0  | 0  | 0  |
| Diastolic Blood Pressure <50 mmHg (n=25,49,8,16) | 22   | 44   | 4  | 10   |
| Diastolic Blood Pressure >90 mmHg(n=25,49,8,16)  | 5  | 8  | 1  | 2  |
| Diastolic Blood Pressure >100 mmHg(n=25,49,8,16) | 2  | 0  | 0  | 1  |
| Respiratory Rate >20 breaths/min (n=25,50,8,16)  | 25   | 50   | 8  | 16   |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Part B: Change From Baseline in Growth Parameters (Body Height)**

|                 |   |
|-----------------|---|
| End point title | Part B: Change From Baseline in Growth Parameters (Body Height) <sup>[78]</sup> |
|-----------------|---|

**End point description:**

Body height was measured for all participants (infantile-onset and later-onset SMA). Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated.

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

End point timeframe:

Baseline, Day 302

Notes:

[78] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed          | 1  | 4  | 1  | 8  |
| Units: cm                            |  |  |  |  |
| arithmetic mean (standard deviation) | 8.00 (± 99999)                                   | 10.25 (± 2.217)                                  | 11.2 (± 99999)                               | 6.9 (± 3.65)                                 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Head Circumference)

|                 |  |
|-----------------|--|
| End point title | Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Head Circumference) <sup>[79]</sup> |
|-----------------|--|

End point description:

Head circumference was measured in participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[79] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group                                  |  |  |
| Number of subjects analysed          | 13   | 35   |  |  |
| Units: cm                            |  |  |  |  |
| arithmetic mean (standard deviation) | 4.52 (± 1.703)                                   | 5.50 (± 2.766)                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Chest Circumference)

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Chest Circumference) <sup>[80]</sup> |
|-----------------|---|

End point description:

Chest circumference was measured in participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[80] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 13  | 35  |  |  |
| Units: cm                            |   |   |  |  |
| arithmetic mean (standard deviation) | 5.67 (± 4.868)  | 6.64 (± 6.362)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Arm Circumference)

|                 |   |
|-----------------|---|
| End point title | Part B Infantile-onset SMA: Change From Baseline in Growth Parameters (Arm Circumference) <sup>[81]</sup> |
|-----------------|---|

End point description:

Arm circumference was measured in participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[81] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

|                                      |   |   |  |  |
|--------------------------------------|---|---|--|--|
| <b>End point values</b>              | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 13  | 35  |  |  |
| Units: cm                            |   |   |  |  |
| arithmetic mean (standard deviation) | 0.45 (± 2.141)  | 1.16 (± 2.144)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Later-onset SMA: Change From Baseline in Growth Parameters (Ulnar Length)

|                 |  |
|-----------------|--|
| End point title | Part B Later-onset SMA: Change From Baseline in Growth Parameters (Ulnar Length) <sup>[82]</sup> |
|-----------------|--|

End point description:

Ulnar length was measured in participants with later-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[82] - 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: Part B Later-onset SMA arms were planned to be analysed for this end point.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Part B: Later-Onset SMA:<br>12/12 mg<br>Nusinersen | Part B: Later-Onset SMA:<br>50/28 mg<br>Nusinersen |  |  |
| Subject group type                   | Reporting group                                    | Reporting group                                    |  |  |
| Number of subjects analysed          | 5  | 16   |  |  |
| Units: cm                            |  |  |  |  |
| arithmetic mean (standard deviation) | 2.8 (± 4.16)                                       | 1.2 (± 1.39)                                       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Change From Baseline in Growth Parameters (Weight for Age Percentile)

|                 |   |
|-----------------|---|
| End point title | Part B: Change From Baseline in Growth Parameters (Weight for Age Percentile) <sup>[83]</sup> |
|-----------------|---|

End point description:

WHO child growth standards (WHO Child Growth Standards, 2006) was used to calculate the weight for age percentile in the infantile-onset participants. The 2000 CDC Growth Charts was used to calculate the weight for age percentile for later-onset participants. Safety set included all participants who received at

least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 302    |           |

Notes:

[83] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed          | 13   | 35   | 7  | 16   |
| Units: percentile                    |  |  |  |  |
| arithmetic mean (standard deviation) | -6.70 (± 23.133)                                 | -3.60 (± 35.202)                                 | 9.1 (± 20.23)                                | -0.3 (± 6.96)                                |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Change From Baseline in Growth Parameters (Weight for Length Percentile)

|                 |  |
|-----------------|--|
| End point title | Part B: Change From Baseline in Growth Parameters (Weight for Length Percentile) <sup>[84]</sup> |
|-----------------|--|

End point description:

As pre-specified in the protocol, weight for length percentile was assessed only for the participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 302    |           |

Notes:

[84] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed          | 12   | 30   | 0 <sup>[85]</sup>                            | 0 <sup>[86]</sup>                            |
| Units: percentile                    |  |  |  |  |
| arithmetic mean (standard deviation) | -4.23 (± 35.817)                                 | 6.05 (± 40.119)                                  | ()   | ()   |

Notes:

[85] - As the number of subjects analyzed was zero, mean and SD was not calculated.

[86] - As the number of subjects analyzed was zero, mean and SD was not calculated.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio)

|                 |   |
|-----------------|---|
| End point title | Part B: Change From Baseline in Growth Parameters (Head-to-Chest Circumference Ratio) <sup>[87]</sup> |
|-----------------|---|

End point description:

As pre-specified in the protocol, head to chest circumference ratio was assessed only for the participants with infantile-onset SMA. Safety set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint. '99999' signifies that since one or no participant was evaluable, SD was not estimated.

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

End point timeframe:

Baseline, Day 302

Notes:

[87] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

|                                      |   |   |  |  |
|--------------------------------------|---|---|--|--|
| <b>End point values</b>              | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen |  |  |
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 13  | 35  |  |  |
| Units: ratio                         |   |   |  |  |
| arithmetic mean (standard deviation) | -0.03 (±<br>0.085)  | -0.05 (±<br>0.269)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (aPTT)

|                 |   |
|-----------------|---|
| End point title | Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (aPTT) <sup>[88]</sup> |
|-----------------|---|

End point description:

aPTT was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of aPTT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of aPTT at baseline to high values postbaseline. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Baseline up to Day 279

Notes:

[88] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values             | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|------------------------------|--|--|--|--|
| Subject group type           | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed  | 25   | 50   | 8  | 16   |
| Units: participants          |  |  |  |  |
| Shift to Low (n=22,48,7,16)  | 4  | 14   | 2  | 2  |
| Shift to High (n=17,40,8,15) | 6  | 7  | 1  | 1  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (PT)

|                 |   |
|-----------------|---|
| End point title | Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (PT) <sup>[89]</sup> |
|-----------------|---|

End point description:

Prothrombin time was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of PT at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of PT at baseline to high values postbaseline. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of the specified parameter.

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

End point timeframe:

Baseline up to Day 279

Notes:

[89] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values             | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|------------------------------|--|--|--|--|
| Subject group type           | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed  | 25   | 50   | 8  | 16   |
| Units: participants          |  |  |  |  |
| Shift to Low (n=22,48,8,15)  | 3  | 6  | 1  | 1  |
| Shift to High (n=20,45,8,14) | 2  | 6  | 0  | 1  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (INR)

|                 |  |
|-----------------|--|
| End point title | Part B: Number of Participants With Shifts From Baseline in Coagulation Parameters (INR) <sup>[90]</sup> |
|-----------------|--|

End point description:

INR was evaluated to assess safety. "Shift to low" measured change in normal, high and unknown values of INR at baseline to low values postbaseline. "Shift to high" measured change in normal, high and unknown values of INR at baseline to high values postbaseline. The category with at least one participant with shift from baseline in INR ratio is reported. Safety set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for analysis of specified parameter.

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

End point timeframe:

Baseline up to Day 279

Notes:

[90] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values             | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|------------------------------|--|--|--|--|
| Subject group type           | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed  | 25   | 50   | 8  | 16   |
| Units: participants          |  |  |  |  |
| Shift to Low (n=22,49,8,16)  | 1  | 5  | 0  | 0  |
| Shift to High (n=21,44,8,16) | 2  | 6  | 1  | 0  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Change From Baseline in Urine Total Protein

|                 |   |
|-----------------|---|
| End point title | Part B: Change From Baseline in Urine Total Protein <sup>[91]</sup> |
|-----------------|---|

End point description:

Safety set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[91] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                     | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed          | 7  | 18   | 3  | 11   |
| Units: g/L                           |  |  |  |  |
| arithmetic mean (standard deviation) | -0.130 ( $\pm$ 0.4126)                           | -3.274 ( $\pm$ 14.1387)                          | -0.213 ( $\pm$ 0.2873)                       | 0.004 ( $\pm$ 0.0608)                        |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements

|                 |  |
|-----------------|--|
| End point title | Part B: Percentage of Participants With a Postbaseline Platelet Count Below the Lower Limit of Normal on at Least 2 Consecutive Measurements <sup>[92]</sup> |
|-----------------|--|

End point description:

Safety set included all participants who received at least one dose of nusinersen.

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

End point timeframe:

Baseline up to Day 302

Notes:

[92] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                  | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed       | 25   | 50   | 8  | 16   |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 4  | 0  | 0  | 0  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Number of Participants With Neurological Examination Abnormalities Reported as AEs

|                 |  |
|-----------------|--|
| End point title | Part B: Number of Participants With Neurological Examination Abnormalities Reported as AEs <sup>[93]</sup> |
|-----------------|--|

End point description:

Participants with abnormalities in neurological examinations recorded as AEs were reported.

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

End point timeframe:

Baseline up to Day 302

Notes:

[93] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values            | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed | 25   | 50   | 8  | 16   |
| Units: participants         |  |  |  |  |
| number (not applicable)     |  |  |  |  |
| Muscular Weakness           | 0  | 1  | 0  | 0  |
| Bulbar Palsy                | 1  | 0  | 0  | 0  |
| Tremor                      | 0  | 0  | 0  | 1  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Percentage of Participants With a Postbaseline QTcF of > 500 msec and an Increase from Baseline to any Postbaseline Timepoint in QTcF of > 60 msec

|                 |  |
|-----------------|--|
| End point title | Part B: Percentage of Participants With a Postbaseline QTcF of > 500 msec and an Increase from Baseline to any Postbaseline Timepoint in QTcF of > 60 msec <sup>[94]</sup> |
|-----------------|--|

End point description:

As a part of safety assessment, QTcF was evaluated for determining the incidence of clinically relevant abnormalities. Post baseline QTcF of > 500 msec and maximum increase from baseline to post baseline QTcF > 60 msec was considered as a criteria for clinically relevant abnormality in ECG. Safety set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Baseline up to Day 302

Notes:

[94] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                  | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed       | 25   | 49   | 8  | 15   |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 8  | 0  | 0  | 0  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A, B and C: Number of Participants With Hospitalizations

|                 |  |
|-----------------|--|
| End point title | Parts A, B and C: Number of Participants With Hospitalizations |
|-----------------|--|

End point description:

Parts A, B and C: ITT set included all participants who received at least one dose of nusinersen in the current study.

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

End point timeframe:

Parts A, B, and C: Baseline up to Day 302

| End point values              | Part A: 28/28 Milligrams (mg) Nusinersen | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                          | Reporting group                                  | Reporting group                                  | Reporting group                              |
| Number of subjects analysed   | 6  | 25   | 50   | 8  |
| Units: number of participants | 1  | 19   | 26   | 3  |

| End point values              | Part B: Later-Onset SMA: 50/28 mg Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|-------------------------------|--|-----------------------------|--|--|
| Subject group type            | Reporting group                              | Reporting group             |  |  |
| Number of subjects analysed   | 16   | 40                          |  |  |
| Units: number of participants | 6  | 12                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Parts A, B and C: Duration of Hospitalizations

|  |  |
|--|--|
| End point title  | Parts A, B and C: Duration of Hospitalizations |
| End point description:<br>Parts A, B and C: ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable for this endpoint. |  |
| End point type   | Secondary                                      |
| End point timeframe:<br>Parts A, B, and C: Baseline up to Day 302  |  |

| End point values              | Part A: 28/28 Milligrams (mg) Nusinersen | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                          | Reporting group                                  | Reporting group                                  | Reporting group                              |
| Number of subjects analysed   | 6  | 25   | 50   | 8  |
| Units: percentage of days     |  |  |  |  |
| median (full range (min-max)) | 0 (0 to 2)                               | 6.4 (0 to 100)                                   | 1.9 (0 to 100)                                   | 0.0 (0 to 8)                                 |

| End point values              | Part B: Later-Onset SMA: 50/28 mg Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|-------------------------------|--|-----------------------------|--|--|
| Subject group type            | Reporting group                              | Reporting group             |  |  |
| Number of subjects analysed   | 16   | 12                          |  |  |
| Units: percentage of days     |  |                             |  |  |
| median (full range (min-max)) | 0.0 (0 to 10)                                | 1.34 (0.3 to 10.4)          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Parts A, B and C: Number of Participants With Clinical Global Impression of Change (CGIC)

|  |   |
|--|---|
| End point title  | Parts A, B and C: Number of Participants With Clinical Global Impression of Change (CGIC) |
| End point description:<br>The CGIC scale was a 7 point scale that required the clinician to assess how much the participant's illness had changed relative to a baseline state at the beginning of the intervention, where 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse. Higher rating indicates worsening of the condition. A separate CGIC assessment was performed by the Investigator (I) and caregiver (C). The categories with at least one participant having a CGIC score was reported. ITT set included all participants who received at least one dose of nusinersen in the current study. 'Subjects analysed' signifies number of participants evaluable for this endpoint. |   |
| End point type   | Secondary   |

End point timeframe:

Parts A, B, and C: Day 302

| End point values            | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 12/12<br>mg Nusinersen | Part B:<br>Infantile-Onset<br>SMA: 50/28<br>mg Nusinersen | Part B: Later-<br>Onset SMA:<br>12/12 mg<br>Nusinersen |
|-----------------------------|---|---|---|--|
| Subject group type          | Reporting group                                   | Reporting group   | Reporting group   | Reporting group  |
| Number of subjects analysed | 6   | 13  | 25  | 7  |
| Units: participants         |   |   |   |  |
| CGIC-I-Very Much Improved   | 0   | 0   | 8   | 0  |
| CGIC-I-Much Improved        | 1   | 10  | 20  | 3  |
| CGIC-I-Minimally Improved   | 5   | 3   | 7   | 4  |
| CGIC-I-No Change            | 0   | 0   | 0   | 0  |
| CGIC-I-Minimally Worse      | 0   | 0   | 0   | 0  |
| CGIC-C-Very Much Improved   | 1   | 3   | 18  | 1  |
| CGIC-C-Much Improved        | 2   | 7   | 13  | 2  |
| CGIC-C-Minimally Improved   | 2   | 3   | 3   | 4  |
| CGIC-C-No Change            | 0   | 0   | 1   | 0  |
| CGIC-C-Minimally Worse      | 1   | 0   | 0   | 0  |

| End point values            | Part B: Later-<br>Onset SMA:<br>50/28 mg<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|-----------------------------|--|--------------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group                |  |  |
| Number of subjects analysed | 16   | 24                             |  |  |
| Units: participants         |  |                                |  |  |
| CGIC-I-Very Much Improved   | 1  | 0                              |  |  |
| CGIC-I-Much Improved        | 5  | 5                              |  |  |
| CGIC-I-Minimally Improved   | 9  | 19                             |  |  |
| CGIC-I-No Change            | 1  | 14                             |  |  |
| CGIC-I-Minimally Worse      | 0  | 2                              |  |  |
| CGIC-C-Very Much Improved   | 0  | 2                              |  |  |
| CGIC-C-Much Improved        | 8  | 6                              |  |  |
| CGIC-C-Minimally Improved   | 7  | 9                              |  |  |
| CGIC-C-No Change            | 1  | 5                              |  |  |
| CGIC-C-Minimally Worse      | 0  | 2                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A, B and C: Number of Serious Respiratory Events

|                 |  |
|-----------------|--|
| End point title | Parts A, B and C: Number of Serious Respiratory Events |
|-----------------|--|

End point description:

ITT set included all participants who received at least one dose of nusinersen in the current study.

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

End point timeframe:

Parts A, B, and C: Baseline up to Day 399

| End point values            | Part A: 28/28 Milligrams (mg) Nusinersen | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                          | Reporting group                                  | Reporting group                                  | Reporting group                              |
| Number of subjects analysed | 6  | 25   | 50   | 8  |
| Units: number of events     |  |  |  |  |
| number (not applicable)     | 0  | 34   | 60   | 6  |

| End point values            | Part B: Later-Onset SMA: 50/28 mg Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|-----------------------------|--|-----------------------------|--|--|
| Subject group type          | Reporting group                              | Reporting group             |  |  |
| Number of subjects analysed | 16   | 40                          |  |  |
| Units: number of events     |  |                             |  |  |
| number (not applicable)     | 2  | 0                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A, B and C: Number of Participants With Ventilator Use

|                 |  |
|-----------------|--|
| End point title | Parts A, B and C: Number of Participants With Ventilator Use |
|-----------------|--|

End point description:

ITT set included all participants who received at least a dose of nusinersen.

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

End point timeframe:

Parts A, B, and C: Screening up to Day 302

| End point values            | Part A: 28/28 Milligrams (mg) Nusinersen | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                          | Reporting group                                  | Reporting group                                  | Reporting group                              |
| Number of subjects analysed | 6  | 25   | 50   | 8  |
| Units: participants         | 0  | 9  | 22   | 4  |

|                             |  |                             |  |  |
|-----------------------------|--|-----------------------------|--|--|
| <b>End point values</b>     | Part B: Later-Onset SMA: 50/28 mg Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
| Subject group type          | Reporting group                              | Reporting group             |  |  |
| Number of subjects analysed | 16   | 40                          |  |  |
| Units: participants         | 5  | 8                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B Infantile-onset SMA: Percentage of Time on Ventilation

|   |   |
|---|---|
| End point title   | Part B Infantile-onset SMA: Percentage of Time on |
| End point description:<br>ITT set included all participants who received at least one dose of nusinersen. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline up to Day 302  |   |

Notes:

[95] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

|                               |  |  |  |  |
|-------------------------------|--|--|--|--|
| <b>End point values</b>       | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |  |  |
| Subject group type            | Reporting group                                  | Reporting group                                  |  |  |
| Number of subjects analysed   | 25   | 50   |  |  |
| Units: percentage of hours    |  |  |  |  |
| median (full range (min-max)) | 5.6 (0 to 100)                                   | 7.5 (0 to 100)                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part A: Change From Baseline in the Parent Assessment of Swallowing Ability (PASA) Scale

|                 |  |
|-----------------|--|
| End point title | Part A: Change From Baseline in the Parent Assessment of Swallowing Ability (PASA) Scale <sup>[96]</sup> |
|-----------------|--|

End point description:

PASA questionnaire was developed to assess the signs and symptoms of dysphagia. It included 33 items across 4 domains. General feeding, drinking liquids and eating solid foods were assessed with 5 levels of response (Never, Rarely, Sometimes, Often, and Always), and 2 items were assessed with 'Yes'/'No'.



The assessment of swallowing concerns has 4 levels of response: Strongly Agree, Agree, Disagree, and Strongly Disagree. Higher score indicates improvement. ITT set included all participants who received at least one dose of nusinersen.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 302    |           |

Notes:

[96] - 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: Part A arm was planned to be analysed for this endpoint.

| End point values                          | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen |  |  |  |
|---|---|--|--|--|
| Subject group type                        | Reporting group                                   |  |  |  |
| Number of subjects analysed               | 6   |  |  |  |
| Units: score on scale                     |   |  |  |  |
| arithmetic mean (standard deviation)      |   |  |  |  |
| Had Difficulty Feeding Themselves         | 0.2 (± 0.41)                                      |  |  |  |
| Had to Suction Excess Saliva/Drool        | 0.0 (± 0.00)                                      |  |  |  |
| Not Able Eat as Much as Would Like        | 0.2 (± 0.41)                                      |  |  |  |
| Not Able Eat Food Variety Would Like      | -0.2 (± 0.41)                                     |  |  |  |
| Been Tube-Fed                             | 0.0 (± 0.00)                                      |  |  |  |
| Attempted to Drink Liquid Foods           | 0.0 (± 0.00)                                      |  |  |  |
| Refused Liquid Foods                      | 0.0 (± 0.00)                                      |  |  |  |
| Difficulty Drinking Thin Liquids          | 0.0 (± 0.00)                                      |  |  |  |
| Difficulty Drinking Thick Liquids         | 0.0 (± 0.00)                                      |  |  |  |
| Cough/Clear Throat Swallow Liquid Food    | 0.0 (± 0.00)                                      |  |  |  |
| Gagged or Choked on Liquid Food           | 0.0 (± 0.00)                                      |  |  |  |
| Retching/Vomiting Drinking Liquids        | 0.0 (± 0.00)                                      |  |  |  |
| Taken > 30 Minutes Drink Liquids          | 0.0 (± 0.00)                                      |  |  |  |
| Attempted to Eat Solid Foods              | 0.0 (± 0.00)                                      |  |  |  |
| Refused Solid Foods                       | 0.2 (± 0.41)                                      |  |  |  |
| Difficulty Swallowing Soft Foods          | 0.0 (± 0.00)                                      |  |  |  |
| Difficulty Swallowing Solid Foods         | -0.2 (± 0.41)                                     |  |  |  |
| Had Difficulty Swallowing Pills           | 0.2 (± 0.98)                                      |  |  |  |
| Cough/Clear Throat Eat/Swallow Solid Food | 0.2 (± 0.41)                                      |  |  |  |
| Had Food Stuck in Throat/Chest            | 0.0 (± 0.00)                                      |  |  |  |
| Gagged/Choked on Their Solid Food         | 0.2 (± 0.41)                                      |  |  |  |
| Retching/Vomiting Eating Solids           | 0.2 (± 0.41)                                      |  |  |  |
| Required Food to Be Cut Up                | 0.7 (± 1.21)                                      |  |  |  |
| Experienced/Shown Pain When Eating        | 0.0 (± 0.00)                                      |  |  |  |
| Has Taken > 30 Minutes Eat Solids         | 0.3 (± 0.52)                                      |  |  |  |
| Concern Child's Swallowing Ability        | 0.8 (± 1.72)                                      |  |  |  |
| Concerned About Child's Weight            | 1.2 (± 1.60)                                      |  |  |  |
| Concern Variety Foods Child Eats          | 0.7 (± 1.51)                                      |  |  |  |
| Concern Child Not Able Eat as Much        | 1.3 (± 1.51)                                      |  |  |  |
| Concern Child Unable Eat Variety          | 1.3 (± 1.37)                                      |  |  |  |
| Concern Not Get Goodness From Diet        | 1.8 (± 1.17)                                      |  |  |  |
| Concerned Child Aspirating Food           | 1.0 (± 1.55)                                      |  |  |  |
| Concern Child Choking When Eating         | 1.2 (± 1.60)                                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Change From Baseline in the PASA Scale

|                 |  |
|-----------------|--|
| End point title | Part B: Change From Baseline in the PASA Scale <sup>[97]</sup> |
|-----------------|--|

End point description:

PASA questionnaire was developed to assess the signs and symptoms of dysphagia. It included 33 items across 4 domains. General feeding, drinking liquids and eating solid foods were assessed with 5 levels of response (Never, Rarely, Sometimes, Often, and Always), and 2 items were assessed with 'Yes'/'No'. The assessment of swallowing concerns has 4 levels of response: Strongly Agree, Agree, Disagree, and Strongly Disagree. As pre-specified in statistical analysis plan (SAP), PASA scale was assessed for the domain General feeding only. Higher score indicates improvement. ITT set included all participants who received at least one a dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint. 'Number analysed (n)', signifies the number of participants evaluable for the specified parameter.

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

End point timeframe:

Baseline, Day 302

Notes:

[97] - 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: Part B Infantile-onset SMA and Part B Later-onset SMA arms were planned to be analysed for this end point.

| End point values                               | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen | Part B: Later-Onset SMA: 12/12 mg Nusinersen | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|--|--|--|--|--|
| Subject group type                             | Reporting group                                  | Reporting group                                  | Reporting group                              | Reporting group                              |
| Number of subjects analysed                    | 7  | 32   | 7  | 14   |
| Units: score on scale                          |  |  |  |  |
| arithmetic mean (standard deviation)           |  |  |  |  |
| Had Difficulty Feeding Themselves (n=7,29)     | -1.6 (± 1.81)                                    | -0.6 (± 1.55)                                    | -0.4 (± 0.53)                                | 0.3 (± 0.73)                                 |
| Had To Suction Excess Saliva or Drool(n=7,31)  | -1.7 (± 1.38)                                    | -0.2 (± 1.58)                                    | 0.1 (± 0.38)                                 | 0.1 (± 0.36)                                 |
| Not Able To Eat As Much As Would Like(n=7,31)  | -1.6 (± 1.72)                                    | -0.2 (± 1.45)                                    | 0.3 (± 0.95)                                 | 0.0 (± 0.39)                                 |
| Not Able To Eat Food Variety They Like(n=7,29) | -1.6 (± 1.72)                                    | -1.0 (± 1.18)                                    | 0.1 (± 0.69)                                 | -0.4 (± 0.93)                                |
| Been Tube-Fed                                  | -1.8 (± 2.11)                                    | -0.9 (± 1.76)                                    | 0.0 (± 0.00)                                 | 0.0 (± 0.00)                                 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Infantile SMA-onset: Change From (Ratio to) Baseline in CSF Concentration of NF-L

|                 |   |
|-----------------|---|
| End point title | Part B: Infantile SMA-onset: Change From (Ratio to) Baseline in CSF Concentration of NF-L <sup>[98]</sup> |
|-----------------|---|

End point description:

The change from baseline data was reported in terms of geometric mean ratio to baseline. Lower ratios to baseline represent greater reductions in concentrations of NF-L from baseline. ITT set included all participants who received at least one dose of nusinersen.

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

End point timeframe:

Baseline, Day 279

Notes:

[98] - 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: Part B Infantile-onset SMA arms were planned to be analysed for this end point.

| End point values                         | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |  |  |
|--|--|--|--|--|
| Subject group type                       | Reporting group                                  | Reporting group                                  |  |  |
| Number of subjects analysed              | 25   | 50   |  |  |
| Units: pg/mL                             |  |  |  |  |
| geometric mean (confidence interval 95%) | 0.06 (0.05 to 0.08)                              | 0.05 (0.04 to 0.06)                              |  |  |

## Statistical analyses

| Statistical analysis title              | Change From Baseline in NF-L CSF Concentration  |
|---|---|
| Comparison groups                       | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen v Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
| Number of subjects included in analysis | 75  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.3785 <sup>[99]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | LS geometric mean ratio   |
| Point estimate                          | 0.86  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.62  |
| upper limit                             | 1.2   |

Notes:

[99] - ANCOVA model was used with treatment as a fixed effect and adjustment for each participant disease duration at screening, baseline log CSF NF-L and baseline CHOP INTEND total score.

## Secondary: Parts A and C: Change From Baseline in HFMSE Total Score

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Change From Baseline in HFMSE Total Score <sup>[100]</sup> |
|-----------------|---|

End point description:

HFMSE scale was a tool used to assess motor function in children with SMA. The original 20 item Hammersmith Functional Motor Scale was expanded to include 13 additional adapted items from the

Gross Motor Function Measure to improve sensitivity for the higher functioning ambulant population. Each item is scored 0 (unable), 1 (performs with modification or adaptation) or 2 (able) and the total score was calculated by summing the 33 items and ranged from 0 to 66 with higher scores indicating greater motor function. ITT set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable in this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[100] - 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: Parts A and C arms were planned to be analysed for this end point.

|                                      |  |                             |  |  |
|--------------------------------------|--|-----------------------------|--|--|
| <b>End point values</b>              | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
| Subject group type                   | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed          | 6  | 38                          |  |  |
| Units: score on scale                |  |                             |  |  |
| arithmetic mean (standard deviation) | -0.8 (± 3.76)                            | 1.8 (± 3.99)                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A and C: Change From Baseline in RULM Total Score

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Change From Baseline in RULM Total Score <sup>[101]</sup> |
|-----------------|--|

End point description:

The RULM Test was used in participants 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 had a total of 20 items with an entry item that served as functional class identification and did not contribute to the total score. The remaining 19 scorable items reflected different functional domains and were graded on a 3-point system with a score of 0 (unable), 1 (able, with modification), and a maximum of 2 (able, no difficulty). Scorable items were summed for a total score range of 0-37, with higher scores indicating increased great upper limb function. ITT set included all participants who received at least one dose of nusinersen. 'Subjects analysed' signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[101] - 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: Parts A and C arms were planned to be analysed for this end point.

|                             |  |                             |  |  |
|-----------------------------|--|-----------------------------|--|--|
| <b>End point values</b>     | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
| Subject group type          | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed | 6  | 37                          |  |  |
| Units: score on scale       |  |                             |  |  |

|                                      |              |              |  |  |
|--------------------------------------|--------------|--------------|--|--|
| arithmetic mean (standard deviation) | 1.5 (± 1.52) | 1.2 (± 2.14) |  |  |
|--------------------------------------|--------------|--------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A and C: Total Number of New WHO Motor Milestones

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Total Number of New WHO Motor Milestones <sup>[102]</sup> |
|-----------------|--|

End point description:

The WHO motor milestones were a set of six milestones in motor development: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone and walking alone. The examiner recorded an overall rating of the participant's emotional state and then for each milestone one of the following four classifications: no (inability) - child tried but failed to perform the milestone, no (refusal) - child refused to perform despite being calm and alert, yes - child was able to perform the milestone, unable to test - could not be tested because of irritability, drowsiness or sickness. ITT set included all participants who received at least one dose of nusinersen. 'Number analysed (n)' signifies number of participants evaluable for this outcome measure.

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

End point timeframe:

Parts A and C: Baseline up to Day 302

Notes:

[102] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                              | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|---|--|-----------------------------|--|--|
| Subject group type                            | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed                   | 6  | 40                          |  |  |
| Units: motor milestones                       |  |                             |  |  |
| Gain of one or More Motor Milestones (n=6,37) | 0  | 3                           |  |  |
| No Change (n=6,37)                            | 0  | 32                          |  |  |
| Loss of one or More Motor Milestones (n=6,37) | 0  | 2                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A and C: Change From Baseline in ACEND Total Score

|                 |   |
|-----------------|---|
| End point title | Parts A and C: Change From Baseline in ACEND Total Score <sup>[103]</sup> |
|-----------------|---|

End point description:

This assessment instrument was designed to quantify the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA. ACEND included domains assessing physical impact (including feeding/grooming/dressing, sitting/play,

transfers, and mobility) and general caregiver impact (including time, emotion, and finance) and each domain comprises several items. The total score ranges from 0 to 100 with a higher score indicating a greater impact on the caregiver. A negative change from baseline indicates an increase in impact on caregiver. ITT set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[103] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                      | Part A: 28/28 Milligrams (mg) Nusinersen | Part C: 50/28 mg Nusinersen |  |  |
|---------------------------------------|--|-----------------------------|--|--|
| Subject group type                    | Reporting group                          | Reporting group             |  |  |
| Number of subjects analysed           | 6  | 17                          |  |  |
| Units: score on scale                 |  |                             |  |  |
| arithmetic mean (standard deviation)  |  |                             |  |  |
| Feeding/Grooming/Dressing Total Score | 0.6 (± 2.51)                             | 0.8 (± 7.50)                |  |  |
| Sitting/Play Total Score              | 0.0 (± 11.03)                            | -2.8 (± 14.48)              |  |  |
| Transfers Total Score                 | -8.0 (± 12.39)                           | -2.0 (± 15.34)              |  |  |
| Mobility Total Score                  | 7.1 (± 13.85)                            | -0.8 (± 15.01)              |  |  |
| Time Total Score                      | 6.3 (± 14.25)                            | 0.4 (± 10.47)               |  |  |
| Emotion Total Score                   | 11.1 (± 7.66)                            | -2.4 (± 9.44)               |  |  |
| Finance Total Score                   | 15.8 (± 14.29)                           | -2.4 (± 12.00)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts A and C: Change From Baseline in PedsQL™ Total Score

|                 |  |
|-----------------|--|
| End point title | Parts A and C: Change From Baseline in PedsQL™ Total |
|-----------------|--|

End point description:

PedsQL was used to measure health related quality of life (HRQOL) in children & adolescents. PedsQL generic core scale included assessment of physical functioning, emotional functioning, social functioning, and school functioning [PedsQL Inventory total score (PQLI)] and PedsQL Neuromuscular Module [Neuromuscular total score (PQLN)] measured HRQOL dimensions specific to with neuromuscular disorders, including SMA. Four dimensions were collected, each item scored on a 5-point ordinal scale (0=Never to 4=Almost Always). Items were reversed scored and were linearly transformed to a 0-100 scale. Total scale score was calculated as sum of all items over number of items answered on all scales. If more than 50% of items or more were missing, scale score was not computed. Higher scores indicated better health related quality of life. ITT set. Subjects analysed: number of participants evaluable for this endpoint. 'Number analysed (n)': number of participants evaluable for this endpoint.

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

End point timeframe:

Parts A and C: Baseline, Day 302

Notes:

[104] - 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: Parts A and C arms were planned to be analysed for this end point.

| End point values                     | Part A: 28/28<br>Milligrams<br>(mg)<br>Nusinersen | Part C: 50/28<br>mg Nusinersen |  |  |
|--------------------------------------|---|--------------------------------|--|--|
| Subject group type                   | Reporting group                                   | Reporting group                |  |  |
| Number of subjects analysed          | 5   | 14                             |  |  |
| Units: score on scale                |   |                                |  |  |
| arithmetic mean (standard deviation) |   |                                |  |  |
| PQLI-Total Score-Subject (n=5,12)    | 6.1 (± 18.28)                                     | 1.1 (± 9.74)                   |  |  |
| PQLI-Total Score-Parent (n=5,14)     | 3.3 (± 12.51)                                     | 0.7 (± 8.15)                   |  |  |
| PQLN-Total Score-Subject (n=5,12)    | 9.9 (± 6.94)                                      | 6.7 (± 13.11)                  |  |  |
| PQLN-Total Score-Parent (n=6,13)     | 4.7 (± 5.72)                                      | 0.1 (± 9.65)                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part C: Change From Baseline in CHOP-INTEND Total Score

|                 |  |
|-----------------|--|
| End point title | Part C: Change From Baseline in CHOP-INTEND Total Score <sup>[105]</sup> |
|-----------------|--|

End point description:

The CHOP-INTEND test was designed to evaluate the motor skills of infants with significant motor weakness. It included 16 items (capturing neck, trunk, and proximal and distal limb strength), nine of which were scored 0, 1, 2, 3, or 4, five were scored as 0, 2, or 4, one was scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4 with greater scores indicating greater muscle strength. Total score ranged from 0 (worst possible score) and 64 (best possible score). ITT set included all participants who received at least one dose of nusinersen in the current study. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated. Subjects analysed signifies number of participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 302

Notes:

[105] - 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: Part C arm was planned to be analysed for this endpoint.

| End point values                     | Part C: 50/28<br>mg Nusinersen |  |  |  |
|--------------------------------------|--------------------------------|--|--|--|
| Subject group type                   | Reporting group                |  |  |  |
| Number of subjects analysed          | 1                              |  |  |  |
| Units: score on scale                |                                |  |  |  |
| arithmetic mean (standard deviation) | 0.0 (± 99999)                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Part C: Change From Baseline in HINE Section 2 Motor Milestones Total Score

|                 |  |
|-----------------|--|
| End point title | Part C: Change From Baseline in HINE Section 2 Motor Milestones Total Score <sup>[106]</sup> |
|-----------------|--|

End point description:

Section 2 of the HINE was used to assess motor milestones of the participants. Its composed of 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each of these categories, participants can progress from complete absence of a motor ability (the lowest level in each category) through multiple milestones (2 to 4 levels in each category) to the highest level within the category. The 8 categories of HINE Section 2 can be summed to give a total score that ranges from 0 to 26. Safety set included all participants who received at least one dose of nusinersen. Subjects analysed signifies number of participants evaluable for this endpoint. '99999' signifies that since only one participant was evaluable, standard deviation (SD) was not estimated.

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

End point timeframe:

Baseline, Day 302

Notes:

[106] - 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: Part C arm was planned to be analysed for this endpoint.

| End point values                     | Part C: 50/28 mg Nusinersen |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 1                           |  |  |  |
| Units: score on scale                |                             |  |  |  |
| arithmetic mean (standard deviation) | 2.0 (± 99999)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of study (up to 1527 days)

Adverse event reporting additional description:

Safety set included all participants who received at least a dose of nusinersen. MedDRA version 24.0 was applied for Part A, MedDRA version 26.1 was applied for Part B, and MedDRA version 26.0 was applied for Part C.

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

### Dictionary used

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

|                    |            |
|--------------------|------------|
| Dictionary version | 24,26,26.1 |
|--------------------|------------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Part A: Nusinersen 28/28 Milligrams (mg) |
|-----------------------|--|

Reporting group description:

Participants with later-onset SMA received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Part C: Nusinersen 50/28 mg |
|-----------------------|-----------------------------|

Reporting group description:

Participants with infantile and later-onset SMA who had been receiving the approved dose of 12 mg for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen intrathecally on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.

|                       |  |
|-----------------------|--|
| Reporting group title | Part B: Later-Onset SMA: 12/12 mg Nusinersen |
|-----------------------|--|

Reporting group description:

Participants with later-onset SMA received 4 loading doses of 12 mg of nusinersen intrathecally on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

|                       |  |
|-----------------------|--|
| Reporting group title | Part B: Later-Onset SMA: 50/28 mg Nusinersen |
|-----------------------|--|

Reporting group description:

Participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen intrathecally on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

|                       |  |
|-----------------------|--|
| Reporting group title | Part B: Infantile-Onset SMA: 12/12 mg Nusinersen |
|-----------------------|--|

Reporting group description:

Participants with infantile-onset SMA received 4 loading doses of 12 mg of nusinersen intrathecally on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135.

|                       |  |
|-----------------------|--|
| Reporting group title | Part B: Infantile-Onset SMA: 50/28 mg Nusinersen |
|-----------------------|--|

Reporting group description:

Participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen intrathecally on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183.

| Serious adverse events                            | Part A: Nusinersen 28/28 Milligrams (mg) | Part C: Nusinersen 50/28 mg | Part B: Later-Onset SMA: 12/12 mg Nusinersen |
|---|--|-----------------------------|--|
| Total subjects affected by serious adverse events |  |                             |  |
| subjects affected / exposed                       | 1 / 6 (16.67%)                           | 6 / 40 (15.00%)             | 4 / 8 (50.00%)                               |
| number of deaths (all causes)                     | 0  | 0                           | 0  |
| number of deaths resulting from                   | 0  | 0                           | 0  |

|  |               |                |                |
|--|---------------|----------------|----------------|
| adverse events                                       |               |                |                |
| Vascular disorders                                   |               |                |                |
| Shock haemorrhagic                                   |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Pregnancy, puerperium and perinatal conditions       |               |                |                |
| Abortion spontaneous                                 |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |               |                |                |
| Pyrexia  |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Gait disturbance                                     |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Sudden infant death syndrome                         |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Organ failure  |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |               |                |                |
| Atelectasis  |               |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0          |
| Aspiration   |               |                |                |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Acute respiratory failure                       |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Chronic respiratory failure                     |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cough   |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Interstitial lung disease                       |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Obstructive airways disorder                    |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Respiratory acidosis                            |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Respiratory arrest                              |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Respiratory disorder                            |               |                |               |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory distress                            |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Asthma  |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Oxygen saturation decreased                     |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Electrocardiogram qt prolonged                  |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Fall  |                |                |                |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 2 / 40 (5.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Femur fracture                                  |                |                |                |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 2 / 40 (5.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Traumatic haemothorax                           |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Tracheostomy malfunction                        |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardiac disorders                               |               |                |               |
| Cardiac arrest                                  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardiomyopathy                                  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardio-respiratory arrest                       |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nervous system disorders                        |               |                |               |
| Hypoglycaemic seizure                           |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cerebral infarction                             |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Brain stem infarction                           |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Hypoxic-ischaemic encephalopathy<br>subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders                            |               |                |               |
| Leukocytosis  |               |                |               |
| subjects affected / exposed                                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders                                      |               |                |               |
| Dysphagia   |               |                |               |
| subjects affected / exposed                                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue<br>disorders              |               |                |               |
| Acquired macrocephaly   |               |                |               |
| subjects affected / exposed                                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Muscular weakness   |               |                |               |
| subjects affected / exposed                                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Infections and infestations                                     |               |                |               |
| Adenoviral upper respiratory<br>infection                       |               |                |               |
| subjects affected / exposed                                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Bronchiolitis   |               |                |               |
| subjects affected / exposed                                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0         | 0 / 0          | 0 / 0         |
| Covid-19  |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Enterovirus infection                           |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Escherichia urinary tract infection             |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastroenteritis adenovirus                      |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastroenteritis bacterial                       |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastroenteritis escherichia coli                |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Human coronavirus OC43 infection                |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Lower respiratory tract infection viral         |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Measles   |               |                |               |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Norovirus infection                             |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia                                       |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia acinetobacter                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia aspiration                            |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia bacterial                             |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia influenzal                            |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia mycoplasmal                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia pseudomonal                           |               |                |                |



|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia respiratory syncytial viral           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia viral                                 |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Respiratory tract infection                     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Rhinovirus infection                            |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Stoma site infection                            |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Sepsis  |               |                |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Staphylococcal bacteraemia                      |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Staphylococcal sepsis                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia pneumococcal                          |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastroenteritis rotavirus                       |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |               |                |                |
| Hypoglycaemia                                   |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | Part B: Later-Onset<br>SMA: 50/28 mg<br>Nusinersen | Part B: Infantile-Onset<br>SMA: 12/12 mg<br>Nusinersen | Part B: Infantile-Onset<br>SMA: 50/28 mg<br>Nusinersen |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 2 / 16 (12.50%)                                    | 18 / 25 (72.00%)                                       | 30 / 50 (60.00%)                                       |
| number of deaths (all causes)                     | 0  | 6  | 10   |
| number of deaths resulting from                   | 0  | 6  | 10   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| adverse events                                       |                |                |                |
| Vascular disorders                                   |                |                |                |
| Shock haemorrhagic                                   |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pregnancy, puerperium and perinatal conditions       |                |                |                |
| Abortion spontaneous                                 |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Gait disturbance                                     |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Sudden infant death syndrome                         |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          | 0 / 2          |
| Organ failure  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 1          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Atelectasis  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Aspiration   |                |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1          |
| Acute respiratory failure                       |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 3 / 25 (12.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1          |
| Chronic respiratory failure                     |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Cough   |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Interstitial lung disease                       |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1          |
| Obstructive airways disorder                    |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Respiratory acidosis                            |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| Respiratory arrest                              |                |                 |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Respiratory disorder                            |                |                 |                |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory distress                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 1 / 50 (2.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 4 / 25 (16.00%) | 8 / 50 (16.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 5           | 0 / 11          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Asthma  |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 0 / 50 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Investigations                                  |                |                 |                 |
| Oxygen saturation decreased                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 2 / 50 (4.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Electrocardiogram qt prolonged                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 0 / 50 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                |                 |                 |
| Fall  |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 0 / 50 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 0 / 50 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Traumatic haemothorax                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tracheostomy malfunction                        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 3 / 50 (6.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 1          |
| Cardiomyopathy                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Cardio-respiratory arrest                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Hypoglycaemic seizure                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebral infarction                             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Brain stem infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Hypoxic-ischaemic encephalopathy<br>subjects affected / exposed | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 1          | 0 / 0          |
| Blood and lymphatic system disorders                            |                |                |                |
| Leukocytosis  |                |                |                |
| subjects affected / exposed                                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                                      |                |                |                |
| Dysphagia   |                |                |                |
| subjects affected / exposed                                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue<br>disorders              |                |                |                |
| Acquired macrocephaly   |                |                |                |
| subjects affected / exposed                                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Muscular weakness   |                |                |                |
| subjects affected / exposed                                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                                     |                |                |                |
| Adenoviral upper respiratory<br>infection                       |                |                |                |
| subjects affected / exposed                                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchiolitis   |                |                |                |
| subjects affected / exposed                                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 3 / 50 (6.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 1          | 0 / 4          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 1          |
| Covid-19  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Enterovirus infection                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Escherichia urinary tract infection             |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis adenovirus                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis bacterial                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis escherichia coli                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Human coronavirus OC43 infection                |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection viral         |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Measles   |                |                |                |



|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 0 / 50 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Norovirus infection                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 5 / 25 (20.00%) | 7 / 50 (14.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 7           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           | 0 / 1           |
| Pneumonia acinetobacter                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 0 / 50 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 7 / 50 (14.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 9           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia bacterial                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 1 / 50 (2.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia influenzal                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%)  | 1 / 50 (2.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia mycoplasmal                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%)  | 1 / 50 (2.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia pseudomonal                           |                |                 |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia respiratory syncytial viral           |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia viral                                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Respiratory tract infection                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rhinovirus infection                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Stoma site infection                            |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Staphylococcal bacteraemia                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Staphylococcal sepsis                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Pneumonia pneumococcal                          |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis rotavirus                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| Non-serious adverse events   | Part A: Nusinersen<br>28/28 Milligrams<br>(mg) | Part C: Nusinersen<br>50/28 mg | Part B: Later-Onset<br>SMA: 12/12 mg<br>Nusinersen |
|--|--|--------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 4 / 6 (66.67%)                                 | 36 / 40 (90.00%)               | 7 / 8 (87.50%)                                     |
| Vascular disorders   |  |                                |  |
| Lymphoedema  |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 1 / 40 (2.50%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 1                              | 0  |
| Peripheral coldness  |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 1 / 40 (2.50%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 1                              | 0  |
| Hypotension  |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 0 / 40 (0.00%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 0                              | 0  |
| Hypertension   |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 0 / 40 (0.00%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 0                              | 0  |
| Cyanosis   |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 0 / 40 (0.00%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 0                              | 0  |
| General disorders and administration site conditions                                 |  |                                |  |
| Chills   |  |                                |  |
| subjects affected / exposed  | 1 / 6 (16.67%)                                 | 0 / 40 (0.00%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 2  | 0                              | 0  |
| Pyrexia  |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 3 / 40 (7.50%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 3                              | 0  |
| Vaccination site haemorrhage   |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 1 / 40 (2.50%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 1                              | 0  |
| Feeling hot  |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 1 / 40 (2.50%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 1                              | 0  |
| Infusion site rash   |  |                                |  |
| subjects affected / exposed  | 0 / 6 (0.00%)                                  | 1 / 40 (2.50%)                 | 0 / 8 (0.00%)                                      |
| occurrences (all)  | 0  | 1                              | 0  |
| Medical device pain  |  |                                |  |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 1              | 0             |
| Medical device site discomfort                  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 1              | 0             |
| Vaccination site erythema                       |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 1              | 0             |
| Asthenia  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 1              | 0             |
| Vessel puncture site haemorrhage                |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 1              | 0             |
| Oedema  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Medical device site rash                        |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Medical device site hypersensitivity            |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Oedema peripheral                               |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Respiratory complication associated with device |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Immune system disorders                         |               |                |               |
| Mite allergy                                    |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                               | 0             | 1              | 0             |
| Milk allergy                                    |               |                |               |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |               |                |                |
| Cough   |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 1              | 0              |
| Rhinorrhoea                                     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Epistaxis                                       |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Rhinitis allergic                               |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Bronchial obstruction                           |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                               | 0             | 0              | 1              |
| Respiratory failure                             |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Respiratory muscle weakness                     |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Productive cough                                |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Pleural effusion                                |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Interstitial lung disease                       |               |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0             | 0              | 0              |
| Sneezing  |               |                |                |

|                                     |               |                |               |
|-------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Acute respiratory failure           |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Acute respiratory distress syndrome |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Respiratory distress                |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Increased bronchial secretion       |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Atelectasis                         |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Bronchospasm                        |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Pneumothorax                        |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Hypoxia                             |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Decreased bronchial secretion       |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Psychiatric disorders               |               |                |               |
| Dysphoria                           |               |                |               |
| subjects affected / exposed         | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                   | 0             | 0              | 0             |
| Investigations                      |               |                |               |
| CSF pressure increased              |               |                |               |

|                                    |               |                |                |
|------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed        | 0 / 6 (0.00%) | 2 / 40 (5.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 2              | 0              |
| Crystal urine present              |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 2 / 40 (5.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 2              | 0              |
| CSF protein increased              |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 1              | 0              |
| Body height below normal           |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Weight decreased                   |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Staphylococcus test positive       |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                  | 0             | 0              | 1              |
| Bacterial test positive            |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Body temperature increased         |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Electrocardiogram QT prolonged     |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Oxygen saturation decreased        |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Alanine aminotransferase increased |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Blood albumin decreased            |               |                |                |
| subjects affected / exposed        | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0             | 0              | 0              |
| Myocardial necrosis marker         |               |                |                |



|  |                |                  |                |
|--|----------------|------------------|----------------|
| increased                                      |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Blood phosphorus increased                     |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Blood creatinine decreased                     |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Blood creatine phosphokinase increased         |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Blood bicarbonate decreased                    |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Coronavirus test positive                      |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Gamma-glutamyltransferase increased            |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 0                | 0              |
| Injury, poisoning and procedural complications |                |                  |                |
| Procedural pain                                |                |                  |                |
| subjects affected / exposed                    | 2 / 6 (33.33%) | 8 / 40 (20.00%)  | 3 / 8 (37.50%) |
| occurrences (all)                              | 3              | 12               | 5              |
| Procedural headache                            |                |                  |                |
| subjects affected / exposed                    | 1 / 6 (16.67%) | 13 / 40 (32.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                              | 1              | 20               | 0              |
| Anaesthetic complication neurological          |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 1 / 40 (2.50%)   | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 1                | 0              |
| Fall   |                |                  |                |
| subjects affected / exposed                    | 0 / 6 (0.00%)  | 4 / 40 (10.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                              | 0              | 5                | 0              |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Procedural vomiting         |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 40 (7.50%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 4              | 0             |
| Post procedural discomfort  |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 2              | 0             |
| Road traffic accident       |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 40 (5.00%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 2              | 0             |
| Anaesthetic complication    |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Craniocerebral injury       |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Procedural nausea           |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Skin abrasion               |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Foreign body ingestion      |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Post procedural fever       |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Traumatic haematoma         |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Head injury                 |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Femur fracture              |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|  |                     |                      |                    |
|--|---------------------|----------------------|--------------------|
| Periorbital haemorrhage<br>subjects affected / exposed<br>occurrences (all)              | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Post procedural swelling<br>subjects affected / exposed<br>occurrences (all)             | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Neurological procedural complication<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 1 / 40 (2.50%)<br>1  | 0 / 8 (0.00%)<br>0 |
| Post procedural haemorrhage<br>subjects affected / exposed<br>occurrences (all)          | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Congenital, familial and genetic disorders   |                     |                      |                    |
| Cryptorchism<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Developmental hip dysplasia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Cardiac disorders  |                     |                      |                    |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 6 (0.00%)<br>0  | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Nervous system disorders   |                     |                      |                    |
| Headache<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 6 (33.33%)<br>3 | 5 / 40 (12.50%)<br>7 | 0 / 8 (0.00%)<br>0 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 6 (16.67%)<br>2 | 0 / 40 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Balance disorder<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 6 (0.00%)<br>0  | 1 / 40 (2.50%)<br>2  | 0 / 8 (0.00%)<br>0 |

|                                      |               |                |               |
|--------------------------------------|---------------|----------------|---------------|
| Dizziness                            |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 2 / 40 (5.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 2              | 0             |
| Disturbance in attention             |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 1              | 0             |
| Dizziness postural                   |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 1              | 0             |
| Intracranial pressure increased      |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Tremor                               |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Febrile convulsion                   |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Bulbar palsy                         |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Blood and lymphatic system disorders |               |                |               |
| Eosinophilia                         |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Anaemia                              |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Leukocytosis                         |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Iron deficiency anaemia              |               |                |               |
| subjects affected / exposed          | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                    | 0             | 0              | 0             |
| Deficiency anaemia                   |               |                |               |

|                                 |                |                |                |
|---------------------------------|----------------|----------------|----------------|
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Hypofibrinogenaemia             |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Normochromic normocytic anaemia |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Thrombocytosis                  |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Secondary thrombocytosis        |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Ear and labyrinth disorders     |                |                |                |
| Vestibular disorder             |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 1              | 0              |
| Eye disorders                   |                |                |                |
| Myopia                          |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Eye discharge                   |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 0              | 0              |
| Gastrointestinal disorders      |                |                |                |
| Vomiting                        |                |                |                |
| subjects affected / exposed     | 2 / 6 (33.33%) | 1 / 40 (2.50%) | 1 / 8 (12.50%) |
| occurrences (all)               | 2              | 2              | 1              |
| Diarrhoea                       |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 2              | 0              |
| Nausea                          |                |                |                |
| subjects affected / exposed     | 0 / 6 (0.00%)  | 2 / 40 (5.00%) | 0 / 8 (0.00%)  |
| occurrences (all)               | 0              | 2              | 0              |
| Constipation                    |                |                |                |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed            | 0 / 6 (0.00%)  | 2 / 40 (5.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 2              | 0             |
| Abdominal pain                         |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Gastrooesophageal reflux disease       |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Dysphagia                              |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Dysbiosis                              |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Salivary hypersecretion                |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Infantile diarrhoea                    |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Functional gastrointestinal disorder   |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Hepatobiliary disorders                |                |                |               |
| Hyperbilirubinaemia                    |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0             |
| Hepatic function abnormal              |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Skin and subcutaneous tissue disorders |                |                |               |
| Urticaria                              |                |                |               |
| subjects affected / exposed            | 1 / 6 (16.67%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0             |
| Dermatitis allergic                    |                |                |               |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Rash                        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 0              | 1              |
| Dermatitis contact          |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Acne infantile              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Rash erythematous           |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Eczema infantile            |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Dermatitis                  |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Eczema                      |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Dermatitis diaper           |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Renal and urinary disorders |               |                |                |
| Nephrolithiasis             |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Proteinuria                 |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Leukocyturia                |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders |                |                |                |
| Foot deformity                                  |                |                |                |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 2              | 0              | 0              |
| Myalgia   |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 3 / 40 (7.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 5              | 0              |
| Muscle contracture                              |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 3 / 40 (7.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 3              | 0              |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 3 / 40 (7.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 3              | 0              |
| Osteopenia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Joint contracture                               |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 2              | 0              |
| Neck pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 40 (5.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 2              | 0              |
| Limb discomfort                                 |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Musculoskeletal stiffness                       |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Myalgia intercostal                             |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 40 (2.50%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Arthralgia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 2 / 40 (5.00%) | 1 / 8 (12.50%) |
| occurrences (all)                               | 0              | 2              | 1              |
| Osteoporosis                                    |                |                |                |



|                                   |                |                  |                |
|-----------------------------------|----------------|------------------|----------------|
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 40 (2.50%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 1                | 0              |
| Scoliosis                         |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 40 (2.50%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 1                | 0              |
| Short stature                     |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 40 (2.50%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 1                | 0              |
| Tendinous contracture             |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 1 / 40 (2.50%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 1                | 0              |
| Acquired plagiocephaly            |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 0                | 0              |
| Joint range of motion decreased   |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 0                | 0              |
| Muscular weakness                 |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 0                | 0              |
| Extremity contracture             |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 0              | 0                | 0              |
| Infections and infestations       |                |                  |                |
| Upper respiratory tract infection |                |                  |                |
| subjects affected / exposed       | 1 / 6 (16.67%) | 2 / 40 (5.00%)   | 2 / 8 (25.00%) |
| occurrences (all)                 | 2              | 3                | 3              |
| Gingivitis                        |                |                  |                |
| subjects affected / exposed       | 1 / 6 (16.67%) | 0 / 40 (0.00%)   | 0 / 8 (0.00%)  |
| occurrences (all)                 | 1              | 0                | 0              |
| Tonsillitis                       |                |                  |                |
| subjects affected / exposed       | 1 / 6 (16.67%) | 0 / 40 (0.00%)   | 1 / 8 (12.50%) |
| occurrences (all)                 | 1              | 0                | 1              |
| COVID-19                          |                |                  |                |
| subjects affected / exposed       | 0 / 6 (0.00%)  | 11 / 40 (27.50%) | 1 / 8 (12.50%) |
| occurrences (all)                 | 0              | 12               | 1              |

|                             |               |                 |                |
|-----------------------------|---------------|-----------------|----------------|
| Cystitis                    |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Bronchitis                  |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 2               | 0              |
| Gastroenteritis             |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 40 (5.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 2               | 0              |
| Urinary tract infection     |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 40 (5.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 2               | 0              |
| Nasopharyngitis             |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 40 (10.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 6               | 0              |
| Influenza                   |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%)  | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 1               | 1              |
| Sinusitis                   |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 40 (2.50%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Respiratory tract infection |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Asymptomatic bacteriuria    |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Hand-foot-and-mouth disease |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Lice infestation            |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Otitis media acute          |               |                 |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| Suspected COVID-19          |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Vulvovaginal candidiasis    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Vulvovaginitis              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gastroenteritis rotavirus   |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 0              | 1              |
| Otitis media                |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 0              | 1              |
| Pneumonia                   |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 0              | 1              |
| Bronchiolitis               |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Pneumonia klebsiella        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Stoma site infection        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Herpangina                  |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Bronchitis viral            |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Cystitis bacterial          |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |

|  |               |                |               |
|--|---------------|----------------|---------------|
| Enterovirus infection                        |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Eye infection                                |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Helminthic infection                         |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Viral infection                              |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Otitis externa                               |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Pharyngitis                                  |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Pneumonia moraxella                          |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Pneumonia pseudomonal                        |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Respiratory syncytial virus<br>bronchiolitis |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Respiratory tract infection viral            |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Rhinovirus infection                         |               |                |               |
| subjects affected / exposed                  | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                            | 0             | 0              | 0             |
| Sepsis                                       |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Septic shock                            |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Varicella                               |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Vascular device infection               |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Viral upper respiratory tract infection |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Gastroenteritis adenovirus              |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Gastroenteritis Escherichia coli        |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Urinary tract infection enterococcal    |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Staphylococcal infection                |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Pneumonia respiratory syncytial viral   |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Klebsiella urinary tract infection      |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Klebsiella infection                    |               |                |               |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                       | 0             | 0              | 0             |
| Gastroenteritis viral                   |               |                |               |

|                                    |                |                |               |
|------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Gastroenteritis norovirus          |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Acinetobacter infection            |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Conjunctivitis                     |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Enterobacter infection             |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Metabolism and nutrition disorders |                |                |               |
| Decreased appetite                 |                |                |               |
| subjects affected / exposed        | 1 / 6 (16.67%) | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0             |
| Hyponatraemia                      |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Dairy intolerance                  |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Malnutrition                       |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Hypoalbuminaemia                   |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Hypoglycaemia                      |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |
| Hypokalaemia                       |                |                |               |
| subjects affected / exposed        | 0 / 6 (0.00%)  | 0 / 40 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0             |

|   |                    |                     |                    |
|---|--------------------|---------------------|--------------------|
| Lactose intolerance<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |
| Protein deficiency<br>subjects affected / exposed<br>occurrences (all)    | 0 / 6 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 6 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |
| Electrolyte imbalance<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |
| Underweight<br>subjects affected / exposed<br>occurrences (all)           | 0 / 6 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all)       | 0 / 6 (0.00%)<br>0 | 0 / 40 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | Part B: Later-Onset<br>SMA: 50/28 mg<br>Nusinersen | Part B: Infantile-<br>Onset SMA: 12/12<br>mg Nusinersen | Part B: Infantile-<br>Onset SMA: 50/28<br>mg Nusinersen |
|---|--|---|---|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 14 / 16 (87.50%)                                   | 19 / 25 (76.00%)  | 37 / 50 (74.00%)  |
| Vascular disorders  |  |   |   |
| Lymphoedema<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 16 (0.00%)<br>0                                | 0 / 25 (0.00%)<br>0                                     | 0 / 50 (0.00%)<br>0                                     |
| Peripheral coldness<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 16 (0.00%)<br>0                                | 0 / 25 (0.00%)<br>0                                     | 0 / 50 (0.00%)<br>0                                     |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 16 (0.00%)<br>0                                | 0 / 25 (0.00%)<br>0                                     | 1 / 50 (2.00%)<br>1                                     |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 16 (0.00%)<br>0                                | 1 / 25 (4.00%)<br>1                                     | 1 / 50 (2.00%)<br>1                                     |
| Cyanosis  |  |   |   |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 2 / 50 (4.00%)<br>2 |
| General disorders and administration<br>site conditions |                     |                     |                     |
| Chills  |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Pyrexia   |                     |                     |                     |
| subjects affected / exposed                             | 1 / 16 (6.25%)      | 4 / 25 (16.00%)     | 9 / 50 (18.00%)     |
| occurrences (all)                                       | 2                   | 6                   | 12                  |
| Vaccination site haemorrhage                            |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Feeling hot   |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Infusion site rash                                      |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Medical device pain                                     |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Medical device site discomfort                          |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Vaccination site erythema                               |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Asthenia  |                     |                     |                     |
| subjects affected / exposed                             | 10 / 16 (62.50%)    | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Vessel puncture site haemorrhage                        |                     |                     |                     |
| subjects affected / exposed                             | 0 / 16 (0.00%)      | 0 / 25 (0.00%)      | 0 / 50 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Oedema  |                     |                     |                     |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 1 / 50 (2.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Medical device site rash                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 1 / 50 (2.00%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Medical device site hypersensitivity            |                 |                |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 1 / 50 (2.00%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Oedema peripheral                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 1 / 50 (2.00%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Respiratory complication associated with device |                 |                |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 25 (4.00%) | 0 / 50 (0.00%)  |
| occurrences (all)                               | 0               | 1              | 0               |
| Immune system disorders                         |                 |                |                 |
| Mite allergy                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Milk allergy                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 1 / 50 (2.00%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Respiratory, thoracic and mediastinal disorders |                 |                |                 |
| Cough   |                 |                |                 |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 2 / 25 (8.00%) | 5 / 50 (10.00%) |
| occurrences (all)                               | 2               | 2              | 5               |
| Rhinorrhoea                                     |                 |                |                 |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 25 (0.00%) | 0 / 50 (0.00%)  |
| occurrences (all)                               | 2               | 0              | 0               |
| Epistaxis                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Rhinitis allergic                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Bronchial obstruction                           |                 |                |                 |

|                                     |                |                |                |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 2              |
| Respiratory failure                 |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all)                   | 0              | 0              | 3              |
| Respiratory muscle weakness         |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Productive cough                    |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Pleural effusion                    |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Interstitial lung disease           |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Sneezing                            |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Acute respiratory failure           |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Acute respiratory distress syndrome |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Respiratory distress                |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)                   | 0              | 0              | 3              |
| Increased bronchial secretion       |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 2 / 50 (4.00%) |
| occurrences (all)                   | 0              | 1              | 2              |
| Atelectasis                         |                |                |                |
| subjects affected / exposed         | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 2 / 50 (4.00%) |
| occurrences (all)                   | 0              | 1              | 4              |
| Bronchospasm                        |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Pneumothorax<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 16 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2 | 0 / 50 (0.00%)<br>0 |
| Hypoxia<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0 |
| Decreased bronchial secretion<br>subjects affected / exposed<br>occurrences (all)            | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0 |
| Psychiatric disorders<br>Dysphoria<br>subjects affected / exposed<br>occurrences (all)       | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>2 |
| Investigations<br>CSF pressure increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Crystal urine present<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 16 (6.25%)<br>1 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| CSF protein increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Body height below normal<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 16 (6.25%)<br>1 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 16 (6.25%)<br>1 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0 |
| Staphylococcus test positive<br>subjects affected / exposed<br>occurrences (all)             | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Bacterial test positive  |                     |                     |                     |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Body temperature increased             |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Electrocardiogram QT prolonged         |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Oxygen saturation decreased            |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)                      | 0              | 1              | 1              |
| Alanine aminotransferase increased     |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood albumin decreased                |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Myocardial necrosis marker increased   |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all)                      | 0              | 0              | 3              |
| Blood phosphorus increased             |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood creatinine decreased             |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood creatine phosphokinase increased |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Blood bicarbonate decreased            |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Coronavirus test positive              |                |                |                |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 0               | 1              | 0              |
| Gamma-glutamyltransferase increased            |                 |                |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 0               | 1              | 0              |
| Injury, poisoning and procedural complications |                 |                |                |
| Procedural pain                                |                 |                |                |
| subjects affected / exposed                    | 3 / 16 (18.75%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all)                              | 8               | 0              | 3              |
| Procedural headache                            |                 |                |                |
| subjects affected / exposed                    | 4 / 16 (25.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 7               | 0              | 0              |
| Anaesthetic complication neurological          |                 |                |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0              |
| Fall   |                 |                |                |
| subjects affected / exposed                    | 1 / 16 (6.25%)  | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)                              | 1               | 0              | 2              |
| Procedural vomiting                            |                 |                |                |
| subjects affected / exposed                    | 1 / 16 (6.25%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 1               | 0              | 0              |
| Post procedural discomfort                     |                 |                |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                              | 0               | 0              | 3              |
| Road traffic accident                          |                 |                |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0              |
| Anaesthetic complication                       |                 |                |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0              |
| Craniocerebral injury                          |                 |                |                |
| subjects affected / exposed                    | 0 / 16 (0.00%)  | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0              |
| Procedural nausea                              |                 |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Skin abrasion                              |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |
| Foreign body ingestion                     |                |                |                |
| subjects affected / exposed                | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Post procedural fever                      |                |                |                |
| subjects affected / exposed                | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Traumatic haematoma                        |                |                |                |
| subjects affected / exposed                | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Head injury                                |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Femur fracture                             |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Periorbital haemorrhage                    |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Post procedural swelling                   |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Neurological procedural complication       |                |                |                |
| subjects affected / exposed                | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 0              | 1              | 0              |
| Post procedural haemorrhage                |                |                |                |
| subjects affected / exposed                | 1 / 16 (6.25%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                          | 1              | 1              | 0              |
| Congenital, familial and genetic disorders |                |                |                |
| Cryptorchism                               |                |                |                |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                    | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Developmental hip dysplasia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 2 / 50 (4.00%)<br>2 |
| Cardiac disorders   |                     |                     |                     |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 16 (6.25%)<br>1 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Nervous system disorders  |                     |                     |                     |
| Headache<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Balance disorder<br>subjects affected / exposed<br>occurrences (all)                | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all)        | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all)              | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Intracranial pressure increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Tremor  |                     |                     |                     |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 1              | 0              | 0              |
| Febrile convulsion                   |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Bulbar palsy                         |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Blood and lymphatic system disorders |                |                |                |
| Eosinophilia                         |                |                |                |
| subjects affected / exposed          | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                    | 1              | 0              | 1              |
| Anaemia                              |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 3 / 50 (6.00%) |
| occurrences (all)                    | 0              | 1              | 3              |
| Leukocytosis                         |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 2              | 0              |
| Iron deficiency anaemia              |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Deficiency anaemia                   |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 2              | 0              |
| Hypofibrinogenaemia                  |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Normochromic normocytic anaemia      |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Thrombocytosis                       |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Secondary thrombocytosis             |                |                |                |
| subjects affected / exposed          | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |



|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| Ear and labyrinth disorders<br>Vestibular disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0  |
| Eye disorders<br>Myopia<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 16 (6.25%)<br>1  | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0  |
| Eye discharge<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>2  |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 2 / 16 (12.50%)<br>2 | 2 / 25 (8.00%)<br>3 | 4 / 50 (8.00%)<br>6  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 16 (12.50%)<br>2 | 0 / 25 (0.00%)<br>0 | 2 / 50 (4.00%)<br>2  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 16 (0.00%)<br>0  | 1 / 25 (4.00%)<br>2 | 7 / 50 (14.00%)<br>8 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 16 (6.25%)<br>1  | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 16 (0.00%)<br>0  | 1 / 25 (4.00%)<br>1 | 2 / 50 (4.00%)<br>2  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2 | 5 / 50 (10.00%)<br>6 |
| Dysbiosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1  |
| Salivary hypersecretion  |                      |                     |                      |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Infantile diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Functional gastrointestinal disorder<br>subjects affected / exposed<br>occurrences (all)                | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Hepatobiliary disorders<br>Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Hepatic function abnormal<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 2 / 50 (4.00%)<br>3 |
| Skin and subcutaneous tissue disorders<br>Urticaria<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 16 (6.25%)<br>1 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 3 / 50 (6.00%)<br>3 |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 16 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2 | 0 / 50 (0.00%)<br>0 |
| Acne infantile<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0 |
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Eczema infantile  |                     |                     |                     |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Eczema<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 2 / 50 (4.00%)<br>3 |
| Dermatitis diaper<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 3 / 50 (6.00%)<br>3 |
| Renal and urinary disorders<br>Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Leukocyturia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Foot deformity<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Muscle contracture<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0 |
| Osteopenia  |                     |                     |                     |

|                                 |                |                |                |
|---------------------------------|----------------|----------------|----------------|
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Joint contracture               |                |                |                |
| subjects affected / exposed     | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 1              | 0              | 0              |
| Neck pain                       |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Limb discomfort                 |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Musculoskeletal stiffness       |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Myalgia intercostal             |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Arthralgia                      |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Osteoporosis                    |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Scoliosis                       |                |                |                |
| subjects affected / exposed     | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)               | 1              | 0              | 2              |
| Short stature                   |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Tendinous contracture           |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Acquired plagiocephaly          |                |                |                |
| subjects affected / exposed     | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)               | 0              | 0              | 1              |
| Joint range of motion decreased |                |                |                |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  | 1 / 50 (2.00%)<br>1  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  | 1 / 50 (2.00%)<br>1  |
| Extremity contracture<br>subjects affected / exposed<br>occurrences (all)             | 0 / 16 (0.00%)<br>0  | 1 / 25 (4.00%)<br>1  | 0 / 50 (0.00%)<br>0  |
| Infections and infestations   |                      |                      |                      |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 16 (12.50%)<br>2 | 3 / 25 (12.00%)<br>3 | 8 / 50 (16.00%)<br>9 |
| Gingivitis<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 16 (6.25%)<br>1  | 0 / 25 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0  |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 16 (12.50%)<br>2 | 0 / 25 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0  |
| COVID-19<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 16 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2  | 5 / 50 (10.00%)<br>6 |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 16 (6.25%)<br>1  | 3 / 25 (12.00%)<br>3 | 2 / 50 (4.00%)<br>2  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 16 (6.25%)<br>1  | 0 / 25 (0.00%)<br>0  | 1 / 50 (2.00%)<br>2  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 0 / 16 (0.00%)<br>0  | 0 / 25 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 16 (12.50%)<br>2 | 1 / 25 (4.00%)<br>1  | 2 / 50 (4.00%)<br>2  |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Influenza                   |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 25 (4.00%) | 2 / 50 (4.00%) |
| occurrences (all)           | 1              | 1              | 3              |
| Sinusitis                   |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Respiratory tract infection |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 1              | 1              | 1              |
| Asymptomatic bacteriuria    |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Hand-foot-and-mouth disease |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 1              | 0              | 1              |
| Lice infestation            |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Otitis media acute          |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Suspected COVID-19          |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Vulvovaginal candidiasis    |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Vulvovaginitis              |                |                |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Gastroenteritis rotavirus   |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Otitis media                |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)           | 0              | 0              | 2              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Pneumonia                   |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all)           | 0              | 0              | 3              |
| Bronchiolitis               |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)           | 0              | 0              | 2              |
| Pneumonia klebsiella        |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)           | 0              | 0              | 2              |
| Stoma site infection        |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)           | 0              | 0              | 4              |
| Herpangina                  |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 1              | 1              |
| Bronchitis viral            |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Cystitis bacterial          |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Enterovirus infection       |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Eye infection               |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Helminthic infection        |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Viral infection             |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all)           | 0              | 0              | 3              |
| Otitis externa              |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)           | 0              | 0              | 1              |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Pharyngitis                                  |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 0              | 1              |
| Pneumonia moraxella                          |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 0              | 1              |
| Pneumonia pseudomonal                        |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 1              | 1              |
| Respiratory syncytial virus<br>bronchiolitis |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 0              | 1              |
| Respiratory tract infection viral            |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 0              | 1              |
| Rhinovirus infection                         |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 1              | 1              |
| Sepsis                                       |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 1              | 1              |
| Septic shock                                 |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 0              | 1              |
| Varicella                                    |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 1              | 1              |
| Vascular device infection                    |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 0              | 1              |
| Viral upper respiratory tract infection      |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 1 / 50 (2.00%) |
| occurrences (all)                            | 0              | 2              | 1              |
| Gastroenteritis adenovirus                   |                |                |                |



|                                       |                |                |                |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Gastroenteritis Escherichia coli      |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Urinary tract infection enterococcal  |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Staphylococcal infection              |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 2              | 0              |
| Pneumonia respiratory syncytial viral |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Klebsiella urinary tract infection    |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Klebsiella infection                  |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 2              | 0              |
| Gastroenteritis viral                 |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Gastroenteritis norovirus             |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Acinetobacter infection               |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Conjunctivitis                        |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Enterobacter infection                |                |                |                |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences (all)                     | 0              | 1              | 0              |
| Metabolism and nutrition disorders    |                |                |                |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)    | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 0 / 50 (0.00%)<br>0  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1  |
| Dairy intolerance<br>subjects affected / exposed<br>occurrences (all)     | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1  |
| Malnutrition<br>subjects affected / exposed<br>occurrences (all)          | 0 / 16 (0.00%)<br>0 | 2 / 25 (8.00%)<br>3 | 5 / 50 (10.00%)<br>5 |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Lactose intolerance<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Protein deficiency<br>subjects affected / exposed<br>occurrences (all)    | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Electrolyte imbalance<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 50 (0.00%)<br>0  |
| Underweight<br>subjects affected / exposed<br>occurrences (all)           | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1  |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0 | 1 / 50 (2.00%)<br>1 |
|---|---------------------|---------------------|---------------------|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 03 December 2019 | <ul style="list-style-type: none"><li>- Clarified that the primary objective for Part B was to examine efficacy, as measured by the change from baseline in CHOP INTEND total score.</li><li>- Clarified that the remaining assessments that were used to evaluate the clinical efficacy of nusinersen for participants in Part B were secondary endpoints related to a secondary objective.</li><li>- A separate table for Parts A and C objectives and endpoints was added to emphasize the differences between Part B and Parts A and C, and to clarify that safety was the primary objective for Parts A and C.</li></ul>  |
| 05 June 2020     | <ul style="list-style-type: none"><li>- Made revision to the study stopping rules to clarify that they only apply to the primary safety portions of the study.</li><li>- The footnotes regarding ECG monitoring in schedule of activities (SoA) tables were revised to adjust the postdose ECG timing and address abnormal ECG results.</li><li>- The loading dose visit windows for Parts A and B of Study 232SM203 were clarified and revised.</li><li>- A footnote was added to SoA tables to ensure that efficacy assessments (CHOP INTEND, HFMSE, and RULM) were conducted twice prior to the first dose of study treatment.</li><li>- Guidance was added on the number of participants with scoliosis and/or severe contractures to be included in Part C of the study.</li><li>- The study duration was extended, in order to align the requirements of contraception use and reporting, the follow-up period of the study was extended for those participants who require contraception use and an assessment was added on Day 410, Day 420, and Day 382 for Part A, Part B, and Part C, respectively.</li><li>- Inclusion and exclusion criteria was updated.</li><li>- A new section was added to the protocol to provide additional details on ventilation use.</li></ul> |
| 05 August 2020   | <ul style="list-style-type: none"><li>- Made revision to the study stopping rules so that they apply to all participants in Parts A and B of the study.</li><li>- Language was added to the protocol regarding remote monitoring of study sites during the global coronavirus disease (COVID-19) pandemic.</li></ul>   |
| 01 October 2021  | <ul style="list-style-type: none"><li>- Increased the sample size by including an additional cohort of up to approximately 20 adult participants in Part C to allow collection of clinical data in adults transitioning from the currently approved nusinersen dosing regimen to a higher dose.</li><li>- The timepoints for collection of vital signs, neurological examinations, and ECGs and the collection windows for plasma PK samples were updated for Parts B and C.</li><li>- A schedule of activities table specifically for Part C Cohort 2 was added.</li><li>- A new table was added for participants in Part B who discontinued study treatment but agreed to remain in the study for follow-up.</li><li>- Inclusion and exclusion criteria was updated for Parts A,B and C.</li><li>- Added details on contracture assessment, to update the information on PedsQL for the adult participants who enrolled in Cohort 2 of Part C.</li><li>- Updated growth parameters to allow for measurement of length for participants with later-onset SMA who were not able to have height measured.</li></ul>   |

|             |   |
|-------------|---|
| 05 May 2022 | <ul style="list-style-type: none"><li>- Reduced the sample size for Part B infantile onset participants to 75. As a result, the total sample size for the study was adjusted to 145 participants.</li><li>- Part B exclusion criteria was updated.</li><li>- The PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module for participants <math>\geq 26</math> years of age were added.</li><li>- Language was updated in laboratory safety assessments to further specify that total protein would be measured for the CSF local laboratory sample.</li><li>- All references to an interim analysis being performed to assess the feasibility of borrowing participant data from Study CS3B were removed</li></ul> |
|-------------|---|

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported