



Clinical trial results:

A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-002008-25 |
| Trial protocol | GB IT FR |
| Global end of trial date | 25 March 2019 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 |
| This version publication date | 25 September 2020 |
| First version publication date | 25 September 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 4053-101 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02310906 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name | Sarepta Therapeutics, Inc. |
| Sponsor organisation address | 215 First Street, Cambridge, MA, United States, 02142 |
| Public contact | Medical Director, Sarepta Therapeutics, Inc., +1 800-690-2003, clinicaltrials@sarepta.com |
| Scientific contact | Medical Director, Sarepta Therapeutics, Inc., +1 800-690-2003, clinicaltrials@sarepta.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001722-PIP01-14 |
| 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? | No |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 March 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 March 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

PART 1: To evaluate the safety and tolerability of four escalating doses of golodirsén administered once weekly for at least 2 weeks per dose level compared to placebo.

PART 2:

- To assess ambulation, endurance, and muscle function as measured by change from Baseline at Week 144 on the 6-Minute Walk Test (6MWT) in treated and untreated subjects.
- To assess the biological activity of golodirsén via dystrophin expression at Week 48 compared to pre-treatment.

Protection of trial subjects:

Written informed consent from each subject or subject's parent(s) or legal guardian(s), if applicable, and written assent from each subject, if applicable, were obtained before any study-specific screening or baseline period evaluations were performed. The anonymity of participating subject will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. This study was designed and monitored in accordance with Sponsor procedures, which complied with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 13 January 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 33 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Italy: 8 |
| Worldwide total number of subjects | 39 |
| EEA total number of subjects | 39 |

Notes:

Subjects enrolled per age group

| | |
|----------|---|
| In utero | 0 |
|----------|---|

| | |
|-------------------------------------------|----|
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 35 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 5 sites in the France, Italy, and United Kingdom from 13 January 2015 to 25 March 2019.

Pre-assignment

Screening details:

Study conducted in 2 parts: Part 1 and Part 2. When Part 1 was completed and cumulative safety data was reviewed by an independent Data Safety Monitoring Board (DSMB), Part 2 was conducted.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Part 1 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 1: Placebo |

Arm description:

Participants received placebo-matched to golodirsén intravenous (IV) infusions, once weekly up to 12 weeks in Part 1.

| | |
|----------------------------------------|---------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Placebo |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received placebo-matched to golodirsén IV infusions, once weekly up to 12 weeks in Part 1.

| | |
|------------------|--------------------|
| Arm title | Part 1: Golodirsén |
|------------------|--------------------|

Arm description:

Subjects received golodirsén IV infusions, at four dose levels of 4 milligrams per kilograms (mg/kg) once weekly for 2 weeks, followed by 10 mg/kg once weekly for the next 2 weeks (i.e., up to Week 4), followed by 20 mg/kg once weekly for the next 2 weeks (i.e., up to Week 6), followed by 30 mg/kg once weekly from Week 7 to Week 12 in Part 1.

| | |
|----------------------------------------|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Golodirsén |
| Investigational medicinal product code | SRP-4053 |
| Other name | SRP-4053 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received golodirsén IV infusions at dose levels of 4 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg weekly on weeks 1, 3, 5, 7.

| Number of subjects in period 1 | Part 1: Placebo | Part 1: Golodirsén |
|--------------------------------|------------------|--------------------|
| Started | 4 | 8 |
| Received 4 mg/kg | 0 ^[1] | 8 |
| Received 10 mg/kg | 0 ^[2] | 8 |
| Received 20 mg/kg | 0 ^[3] | 8 |
| Received 30 mg/kg | 0 ^[4] | 8 |
| Completed | 4 | 8 |

Notes:

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

Justification: There were no separate or defined dose level for Placebo.

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

Justification: There were no separate or defined dose level for Placebo.

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

Justification: There were no separate or defined dose level for Placebo.

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

Justification: There were no separate or defined dose level for Placebo.

Period 2

| | |
|------------------------------|----------------------------------------------|
| Period 2 title | Part 2 |
| Is this the baseline period? | Yes ^[5] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Part 2a: Total Golodirsén Group |

Arm description:

All subjects from Part 1 (who previously received placebo or golodirsén) and including additional new subjects received Golodirsén 30 milligram (mg)/kilogram (kg) once weekly, for up to 168 weeks. Dosing was interrupted or halted when any specific predefined stopping criteria was met or if warranted at the discretion of the Sponsor or Investigator.

| | |
|----------------------------------------|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Golodirsén |
| Investigational medicinal product code | SRP-4053 |
| Other name | SRP-4053 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received golodirsén IV infusions, 30 mg/kg weekly, for up to 168 weeks in Part 2.

| | |
|------------------|-----------------------------------------------------------|
| Arm title | Part 2b: Untreated Group (Natural History of Non-exon 53) |
|------------------|-----------------------------------------------------------|

Arm description:

Untreated subjects intended to evaluate the natural history of the disease with DMD and various genetic

mutations (not amenable to exon 53 skipping) were included in this group and did not received any treatment. Subjects underwent the same study assessments as treated subjects in other reporting groups (except for pharmacokinetic [PK] sampling and muscle biopsies), but at a reduced schedule through Week 144. Thus, the untreated subjects are not considered a control group.

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

Notes:

[5] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: 12 subjects of part 1 were involved in the part 2 of the study (Total Golodirsén Group).

Hence, the part 2 of the study was considered as the baseline period.

| Number of subjects in period 2 | Part 2a: Total Golodirsén Group | Part 2b: Untreated Group (Natural History of Non-exon 53) |
|----------------------------------------|---------------------------------|-----------------------------------------------------------|
| | | |
| Started | 25 | 14 |
| Completed | 23 | 6 |
| Not completed | 2 | 8 |
| Consent withdrawn by subject | 2 | 4 |
| Personal reasons | - | 1 |
| Lost to follow-up | - | 1 |
| Due to enrollment in therapeutic study | - | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Reporting group title | Part 2a: Total Golodirsén Group |
| Reporting group description: | |
| All subjects from Part 1 (who previously received placebo or golodirsén) and including additional new subjects received Golodirsén 30 milligram (mg)/kilogram (kg) once weekly, for up to 168 weeks. Dosing was interrupted or halted when any specific predefined stopping criteria was met or if warranted at the discretion of the Sponsor or Investigator. | |
| Reporting group title | Part 2b: Untreated Group (Natural History of Non-exon 53) |
| Reporting group description: | |
| Untreated subjects intended to evaluate the natural history of the disease with DMD and various genetic mutations (not amenable to exon 53 skipping) were included in this group and did not received any treatment. Subjects underwent the same study assessments as treated subjects in other reporting groups (except for pharmacokinetic [PK] sampling and muscle biopsies), but at a reduced schedule through Week 144. Thus, the untreated subjects are not considered a control group. | |

| Reporting group values | Part 2a: Total Golodirsén Group | Part 2b: Untreated Group (Natural History of Non-exon 53) | Total |
|-------------------------------------------|---------------------------------|-----------------------------------------------------------|-------|
| Number of subjects | 25 | 14 | 39 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 8.4 | 8.5 | |
| standard deviation | ± 2.18 | ± 1.91 | - |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 25 | 14 | 39 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Black | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 23 | 11 | 34 |
| Other | 2 | 2 | 4 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 4 | 0 | 4 |
| Not Hispanic or Latino | 9 | 9 | 18 |
| Unknown or Not Reported | 12 | 5 | 17 |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Reporting group title | Part 1: Placebo |
| Reporting group description: Participants received placebo-matched to golodirsen intravenous (IV) infusions, once weekly up to 12 weeks in Part 1. | |
| Reporting group title | Part 1: Golodirsen |
| Reporting group description: Subjects received golodirsen IV infusions, at four dose levels of 4 milligrams per kilograms (mg/kg) once weekly for 2 weeks, followed by 10 mg/kg once weekly for the next 2 weeks (i.e., up to Week 4), followed by 20 mg/kg once weekly for the next 2 weeks (i.e., up to Week 6), followed by 30 mg/kg once weekly from Week 7 to Week 12 in Part 1. | |
| Reporting group title | Part 2a: Total Golodirsen Group |
| Reporting group description: All subjects from Part 1 (who previously received placebo or golodirsen) and including additional new subjects received Golodirsen 30 milligram (mg)/kilogram (kg) once weekly, for up to 168 weeks. Dosing was interrupted or halted when any specific predefined stopping criteria was met or if warranted at the discretion of the Sponsor or Investigator. | |
| Reporting group title | Part 2b: Untreated Group (Natural History of Non-exon 53) |
| Reporting group description: Untreated subjects intended to evaluate the natural history of the disease with DMD and various genetic mutations (not amenable to exon 53 skipping) were included in this group and did not received any treatment. Subjects underwent the same study assessments as treated subjects in other reporting groups (except for pharmacokinetic [PK] sampling and muscle biopsies), but at a reduced schedule through Week 144. Thus, the untreated subjects are not considered a control group. | |
| Subject analysis set title | Part 1: Placebo |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects received placebo-matched to golodirsen IV infusions, once weekly for up to 12 weeks in Part 1 | |
| Subject analysis set title | Part 1: Golodirsen (4 mg/kg) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects received golodirsen IV infusions, at dose level of 4 mg/kg, once weekly for 2 weeks in Part 1. | |
| Subject analysis set title | Part 1: Golodirsen (10 mg/kg) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects received golodirsen IV infusions, at a dose level of 10 mg/kg, once weekly for the next 2 weeks (i.e., up to Week 4) in Part 1. | |
| Subject analysis set title | Part 1: Golodirsen (20 mg/kg) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects received golodirsen IV infusions, at a dose level of 20 mg/kg, once weekly for the next 2 weeks (i.e., up to Week 6) in Part 1. | |
| Subject analysis set title | Part 1: Golodirsen (30 mg/kg) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects received golodirsen IV infusions, at a dose level of 30 mg/kg, once weekly from Week 7 to Week 12 in Part 1. | |

Primary: Part 1: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Discontinuation

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|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Discontinuation ^[1] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Adverse event (AE) was any untoward medical occurrence in a clinical trial subject, which does not necessarily have a causal relationship with the investigational drug. A Serious adverse event (SAE) was an AE resulting in any of the following outcomes: death; Life-threatening event; Required or prolonged inpatient hospitalization; persistent or significant disability/incapacity; congenital anomaly. TEAEs were defined as AEs that were reported or worsened on or after the start of study drug dosing through 12 weeks. TEAEs included both Serious TEAEs and non-serious TEAEs. Part 1 safety set included all randomised subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline up to Week 12

Notes:

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

Justification: No statistical testing was performed for the primary end point.

| End point values | Part 1: Placebo | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) |
|------------------------------------------------|----------------------|------------------------------|-------------------------------|-------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 8 | 8 | 8 |
| Units: Subjects | | | | |
| Subjects with TEAEs | 4 | 5 | 5 | 3 |
| Subjects with Serious TEAEs | 0 | 0 | 0 | 0 |
| Subjects with TEAEs leading to discontinuation | 0 | 0 | 0 | 0 |

| End point values | Part 1: Golodirsen (30 mg/kg) | | | |
|------------------------------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subjects | | | | |
| Subjects with TEAEs | 6 | | | |
| Subjects with Serious TEAEs | 0 | | | |
| Subjects with TEAEs leading to discontinuation | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Subjects With Potentially Clinically Significant (PCS) Laboratory Abnormalities Reported as TEAEs

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|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Number of Subjects With Potentially Clinically Significant (PCS) Laboratory Abnormalities Reported as TEAEs ^[2] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Laboratory parameters included hematology, serum chemistry (SC), urinalysis and coagulation. Number of subjects with at least one potentially clinically significant abnormal findings were reported as TEAEs. The Investigator determined whether abnormal assessment results were potentially clinically significant or not. Potentially clinical significance was defined as any variation in assessment results that had medical relevance resulting in an alteration in medical care. Part 1 safety set included all randomised subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline up to Week 12

Notes:

[2] - 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: No statistical testing was performed for the primary endpoint.

| End point values | Part 1: Placebo | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) |
|-----------------------------|----------------------|------------------------------|-------------------------------|-------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 8 | 8 | 8 |
| Units: Subjects | | | | |
| Hepatic Chemistry | 0 | 0 | 0 | 0 |
| Renal Chemistry | 0 | 0 | 0 | 0 |
| Hematology | 2 | 0 | 1 | 0 |
| Coagulation | 0 | 0 | 0 | 0 |
| Urinalysis | 0 | 0 | 0 | 0 |

| End point values | Part 1: Golodirsen (30 mg/kg) | | | |
|-----------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subjects | | | | |
| Hepatic Chemistry | 0 | | | |
| Renal Chemistry | 0 | | | |
| Hematology | 0 | | | |
| Coagulation | 0 | | | |
| Urinalysis | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs Reported as TEAEs

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|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs Reported as TEAEs ^[3] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Vital sign parameters included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and body temperature. Number of subjects with at least one potentially clinically significant abnormal vital signs findings were reported as TEAEs. The Investigator determined whether abnormal

assessment results were potentially clinically significant or not. Potential clinical significance was defined as any variation in assessment results that had medical relevance resulting in an alteration in medical care. Part 1 safety set included all randomised subjects who received at least one dose of study drug.

| | |
|------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline up to Week 12 | |

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: No statistical testing was performed for the primary end point.

| End point values | Part 1: Placebo | Part 1: Golodirsén (4 mg/kg) | Part 1: Golodirsén (10 mg/kg) | Part 1: Golodirsén (20 mg/kg) |
|-----------------------------|----------------------|------------------------------|-------------------------------|-------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 8 | 8 | 8 |
| Units: Subjects | 1 | 3 | 1 | 1 |

| End point values | Part 1: Golodirsén (30 mg/kg) | | | |
|-----------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subjects | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Physical Examinations

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Physical Examinations ^[4] |
|-----------------|--------------------------------------------------------------------------------------------------------------------------|

End point description:

Physical examinations were performed by the Investigator, or qualified study staff. A full physical examination included a review of general appearance, head, eyes, ears, nose and throat, heart, lungs, abdomen, extremities, skin, lymph nodes, musculoskeletal, and neurological systems. Number of subjects with potentially clinically significant abnormalities in physical examinations were reported. Potentially clinically significant abnormalities in physical examinations were based on Investigator's discretion. Part 1 safety set included all randomised subjects who received at least one dose of study drug.

| | |
|------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline up to Week 12 | |

Notes:

[4] - 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: No statistical testing was performed for the primary end point.

| End point values | Part 1: Placebo | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) |
|-----------------------------|----------------------|------------------------------|-------------------------------|-------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 8 | 8 | 8 |
| Units: Subjects | 0 | 0 | 2 | 0 |

| End point values | Part 1: Golodirsen (30 mg/kg) | | | |
|-----------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subjects | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Electrocardiogram (ECG) Reported as TEAEs

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Electrocardiogram (ECG) Reported as TEAEs ^[5] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Twelve-lead ECGs were performed at a consistent time of day throughout the study. Electrocardiograms were performed only after the subject was in the supine position, resting, and quiet for a minimum of 15 minutes. The ECG was manually reviewed and interpreted by medically qualified personnel. Number of subjects with potentially clinically significant abnormalities in ECG reported as TEAEs presented here. The Investigator determined whether abnormal assessment results were potentially clinically significant or not. Part 1 safety set included all randomised subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline up to Week 12

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: No statistical testing was performed for the primary end point.

| End point values | Part 1: Placebo | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) |
|-----------------------------|----------------------|------------------------------|-------------------------------|-------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 8 | 8 | 8 |
| Units: Subjects | 0 | 1 | 0 | 0 |

| End point values | Part 1: Golodirsen (30 mg/kg) | | | |
|------------------|-------------------------------|--|--|--|
|------------------|-------------------------------|--|--|--|

| | | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subjects | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Echocardiograms (ECHO)

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Number of Subjects With Potentially Clinically Significant Abnormalities in Echocardiograms (ECHO) ^[6] |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

Standard, 2-dimensional ECHOs were performed at a consistent time of day throughout the study. Cardiac function events included cardiomegaly, tachycardia, and dyspnoea. The ECHO was reviewed and interpreted by medically qualified personnel. Number of subjects with potentially clinically significant abnormalities in ECHO were reported. Part 1 safety set included all randomised subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline up to Week 12

Notes:

[6] - 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: No statistical testing was performed for the primary end point.

| End point values | Part 1: Placebo | Part 1: Golodirsén (4 mg/kg) | Part 1: Golodirsén (10 mg/kg) | Part 1: Golodirsén (20 mg/kg) |
|-----------------------------|----------------------|------------------------------|-------------------------------|-------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 8 | 8 | 8 |
| Units: Subjects | 0 | 0 | 0 | 0 |

| End point values | Part 1: Golodirsén (30 mg/kg) | | | |
|-----------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subjects | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 2a: Change From Baseline in the Total Distance Walked During 6-Minute Walk Test (6MWT) at Week 144 in Total Golodirsén Group

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2a: Change From Baseline in the Total Distance Walked During 6-Minute Walk Test (6MWT) at Week 144 in Total |
|-----------------|------------------------------------------------------------------------------------------------------------------|

End point description:

6MWT was performed by standardized procedures for all subjects. Subjects were asked to walk a set course of 25 meters for 6 minutes (timed), and the distance walked (in meters) was recorded. Change from baseline in 6MWT distance at Week 144 in total golodirsen group was reported. Efficacy Set consisted of all randomized subjects who had at least one post-baseline functional assessment. Here "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 144

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: No statistical testing was performed for the primary end point.

[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: This endpoint was analysed only for Total Golodirsen Group.

| End point values | Part 2a: Total Golodirsen Group | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 | | | |
| Units: meters | | | | |
| arithmetic mean (standard deviation) | -99.0 (± 123.75) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 2a: Change from Baseline in Dystrophin Protein Levels Determined by Western Blot at Week 48 in Total Golodirsen Group

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2a: Change from Baseline in Dystrophin Protein Levels Determined by Western Blot at Week 48 in Total Golodirsen Group ^{[9][10]} |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Change from baseline in dystrophin protein levels (in muscle biopsy samples) were determined by Western blot in total golodirsen group. Muscle biopsy set included all subjects who received at least one dose of study drug and who had data from both baseline (pre-treatment) and Part 2 Week 48 (on-treatment) muscle biopsy samples. Data for this endpoint was not planned to be collected and analysed for untreated group (Natural History of Non-exon 53).

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

End point timeframe:

Baseline, Week 48

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: No statistical testing was performed for the primary end point.

[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: This endpoint was analysed only for Total Golodirsen group.

| | | | | |
|------------------------------------------------|---------------------------------|--|--|--|
| End point values | Part 2a: Total Golodirsén Group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Percent normal dystrophin protein level | | | | |
| arithmetic mean (standard deviation) | 0.924 (\pm 1.0129) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 2b: Change From Baseline in the Total Distance Walked During 6-Minute Walk Test (6MWT) at Week 144 in Untreated Group (Natural History of Non-exon 53)

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2b: Change From Baseline in the Total Distance Walked During 6-Minute Walk Test (6MWT) at Week 144 in Untreated Group (Natural History of Non-exon 53) ^{[11][12]} |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

6MWT was performed by standardized procedures for all subjects. Subjects were asked to walk a set course of 25 meters for 6 minutes (timed), and the distance walked (in meters) was recorded. Change from baseline in 6MWT distance at Week 144 in untreated group (Natural History of Non-exon 53) was reported. Efficacy Set consisted of all randomized subjects who had at least one post-baseline functional assessment. Here "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 144

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: No statistical testing was performed for the primary end point.

[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: This endpoint was analysed only for Untreated Group (Natural History of Non-exon 53).

| | | | | |
|--------------------------------------|-----------------------------------------------------------|--|--|--|
| End point values | Part 2b: Untreated Group (Natural History of Non-exon 53) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: meters | | | | |
| arithmetic mean (standard deviation) | -160.8 (\pm 162.41) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Maximum Plasma Concentration (C_{max}) of Golodirsén

| | |
|-----------------|------------------------------------------------------------------------|
| End point title | Part 1: Maximum Plasma Concentration (C _{max}) of Golodirsén |
|-----------------|------------------------------------------------------------------------|

End point description:

Maximum Concentration (C_{max}) of golodirsén in plasma was evaluated. Pharmacokinetic (PK) set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsén (4 mg/kg) | Part 1: Golodirsén (10 mg/kg) | Part 1: Golodirsén (20 mg/kg) | Part 1: Golodirsén (30 mg/kg) |
|-----------------------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 8 | 8 |
| Units: nanogram per milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 7840 (± 45.7) | 17000 (± 40.9) | 39700 (± 71.8) | 53300 (± 37.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Time to Reach Maximum Plasma Concentration (T_{max}) of Golodirsén

| | |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Part 1: Time to Reach Maximum Plasma Concentration (T _{max}) of Golodirsén |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

Time to reach maximum plasma concentration (T_{max}) of golodirsén was evaluated. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) |
|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 8 | 8 |
| Units: hour | | | | |
| median (full range (min-max)) | 1.11 (0.77 to 1.67) | 1.09 (0.12 to 1.62) | 1.12 (0.80 to 1.58) | 1.12 (0.68 to 1.50) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Area Under the Concentration-Time Curve From Time Zero Extrapolated to the Infinity (AUCinf) of Golodirsen in Plasma

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 1: Area Under the Concentration-Time Curve From Time Zero Extrapolated to the Infinity (AUCinf) of Golodirsen in Plasma |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|

End point description:

Area under the concentration-time curve from time zero extrapolated to the infinity was evaluated. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Here, "number of subjects" analysed signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) |
|-----------------------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 6 | 8 |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 11800 (± 35.5) | 26400 (± 42.7) | 62300 (± 52.6) | 90800 (± 33.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Apparent Volume of Distribution at Steady State (Vss) of Golodirsen

| | |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Part 1: Apparent Volume of Distribution at Steady State (Vss) of Golodirsen |
|-----------------|-----------------------------------------------------------------------------|

End point description:

Volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent

volume of distribution at steady state of golodirsén was evaluated. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Here, "number of subjects" analysed signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsén (4 mg/kg) | Part 1: Golodirsén (10 mg/kg) | Part 1: Golodirsén (20 mg/kg) | Part 1: Golodirsén (30 mg/kg) |
|-----------------------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 6 | 8 |
| Units: liter per kilogram (L/kg) | | | | |
| geometric mean (geometric coefficient of variation) | 0.670 (± 38.6) | 0.767 (± 43.4) | 0.576 (± 84.5) | 0.668 (± 32.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Elimination Half-life (T_{1/2}) of Golodirsén

| | |
|-----------------|-----------------------------------------------------------------|
| End point title | Part 1: Elimination Half-life (T _{1/2}) of Golodirsén |
|-----------------|-----------------------------------------------------------------|

End point description:

T_{1/2} is the time measured for the plasma concentration of drug to decrease by one half. T_{1/2} of golodirsén was evaluated. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Here, "number of subjects" analysed signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsén (4 mg/kg) | Part 1: Golodirsén (10 mg/kg) | Part 1: Golodirsén (20 mg/kg) | Part 1: Golodirsén (30 mg/kg) |
|--------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 6 | 8 |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 2.36 (± 0.581) | 3.63 (± 2.04) | 3.27 (± 0.897) | 3.42 (± 0.628) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Total Clearance (CL) of Golodirsen

| | |
|-----------------|--------------------------------------------|
| End point title | Part 1: Total Clearance (CL) of Golodirsen |
|-----------------|--------------------------------------------|

End point description:

Drug clearance is a quantitative measure of the rate at which a drug substance was removed from the blood. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Here, "number of subjects" analysed signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) |
|--------------------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 6 | 8 |
| Units: liters per hour per kilogram (L/hr/kg) | | | | |
| arithmetic mean (standard deviation) | 0.381 (± 36.0) | 0.405 (± 46.2) | 0.338 (± 52.2) | 0.346 (± 34.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Mean Residence Time (MRT) of Golodirsen

| | |
|-----------------|-------------------------------------------------|
| End point title | Part 1: Mean Residence Time (MRT) of Golodirsen |
|-----------------|-------------------------------------------------|

End point description:

MRT= AUMCinf/AUCinf, where AUMCinf is the area under the first moment curve from time 0 extrapolated to infinite time, calculated using the linear/log trapezoidal method. Mean residence time of golodirsen was evaluated. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Here, "number of subjects" analysed signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

Pre-dose, 5 to 10 minutes, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 hours post-dose at Weeks 1 (for 4 mg/kg arm), 3 (for 10 mg/kg arm), 5 (for 20 mg/kg arm) and 7 (for 30 mg/kg arm)

| End point values | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) |
|--------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 6 | 8 |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 1.79 (± 0.325) | 1.92 (± 0.338) | 1.77 (± 0.495) | 1.95 (± 0.312) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Renal Clearance (CLR) of Golodirsen

| | |
|-----------------|---------------------------------------------|
| End point title | Part 1: Renal Clearance (CLR) of Golodirsen |
|-----------------|---------------------------------------------|

End point description:

Renal clearance was calculated using the partial AUC₀₋₂₄ from the non-compartmental analysis in plasma and AE₀₋₂₄. AUC₀₋₂₄ was defined as area under the plasma concentration-time curve, from time 0 to 24 hours after completion of dosing. AE₀₋₂₄ was defined as total cumulative amount excreted from 0 to 24 hours. Summarized data of all urine collection intervals were reported. PK set consisted of all randomised subjects from Part 1 who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm.

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

End point timeframe:

0 to 1440 min after initiation of dosing on Day 1

| End point values | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) |
|-----------------------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 7 | 8 |
| Units: L/hr/kg | | | | |
| geometric mean (geometric coefficient of variation) | 0.345 (± 31.9) | 0.370 (± 50.6) | 0.355 (± 42.1) | 0.374 (± 26.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2a: Percent Change from Baseline in Forced Vital Capacity Predicted (FVC %p) to Week144 in Total Golodirsen Group

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2a: Percent Change from Baseline in Forced Vital Capacity Predicted (FVC %p) to Week144 in Total Golodirsen Group ^[13] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

FVC is the total amount of air exhaled during the forced expiratory volume test that was measured during spirometry; and was the most important measurement of lung function. This test requires subject to breath into a tube connected to a machine that measures the amount of air that can be

moved in and out of the lungs after taking an inhaled bronchodilator medicine, which was used to dilate subjects bronchial (breathing) tubes. Percent of predicted FVC = (observed value)/ (predicted value) * 100%. Efficacy set consisted of all randomised subjects from Part 1 and all Part 2 subjects who had at least 1 post-baseline functional assessment. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 144

Notes:

[13] - 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: This endpoint was analysed only for Total Golodirsén group.

| | | | | |
|--------------------------------------|---------------------------------|--|--|--|
| End point values | Part 2a: Total Golodirsén Group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -8.382 (± 29.4566) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2a: Change from Baseline in Dystrophin Intensity Levels Determined by Immunohistochemistry (IHC) at Week 48 in Total Golodirsén Group

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2a: Change from Baseline in Dystrophin Intensity Levels Determined by Immunohistochemistry (IHC) at Week 48 in Total Golodirsén Group ^[14] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Change from baseline in dystrophin Intensity levels (in muscle biopsy samples) was determined by Immunohistochemistry in total golodirsén group. Muscle biopsy set included all subjects who received at least 1 dose of study drug and who had data from both baseline (pre-treatment) and Part 2 Week 48 (on-treatment) muscle biopsy samples. Data for this endpoint was not planned to be collected and analysed for untreated group (Natural History of Non-exon 53).

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

End point timeframe:

Baseline, Week 48

Notes:

[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: This endpoint was analysed only for Total Golodirsén group.

| | | | | |
|-------------------------------------------|---------------------------------|--|--|--|
| End point values | Part 2a: Total Golodirsén Group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Percent dystrophin positive fibers | | | | |
| arithmetic mean (standard deviation) | 0.023 (± 0.0243) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2a: Percent Change from Baseline in Exon 53 Skipping Determined by Reverse Transcription Polymerase Chain Reaction (PCR) at Week 48 in Total Golodirsén Group

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2a: Percent Change from Baseline in Exon 53 Skipping Determined by Reverse Transcription Polymerase Chain Reaction (PCR) at Week 48 in Total Golodirsén Group ^[15] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Percent change from baseline in Exon 53 skipping (in muscle biopsy samples) was determined by reverse transcription polymerase chain reaction in total golodirsén group. Muscle biopsy set included all subjects who received at least 1 dose of study drug and who had data from both baseline (pre-treatment) and Part 2 Week 48 (on-treatment) muscle biopsy samples. Data for this endpoint was not planned to be collected and analysed for untreated group (Natural History of Non-exon 53).

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

End point timeframe:

Baseline, Week 48

Notes:

[15] - 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: This endpoint was analysed only for Total Golodirsén group.

| | | | | |
|--------------------------------------|---------------------------------|--|--|--|
| End point values | Part 2a: Total Golodirsén Group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | 16.363 (± 10.6223) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2a: Percent Change from Baseline in Dystrophin Positive Fibers Determined by Immunohistochemistry (IHC) at Week 48 in Total Golodirsén Group

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2a: Percent Change from Baseline in Dystrophin Positive Fibers Determined by Immunohistochemistry (IHC) at Week 48 in Total Golodirsén Group ^[16] |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Percent change from baseline in dystrophin positive fibers (in muscle biopsy samples) were determined by Immunohistochemistry at Week 48 in total golodirsén group. Muscle biopsy set included all subjects who received at least 1 dose of study drug and who had data from both baseline (pre-treatment) and Part 2 Week 48 (on-treatment) muscle biopsy samples. Data for this endpoint was not planned to be

collected and analysed for untreated group (Natural History of Non-exon 53).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 48 | |

Notes:

[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: This endpoint was analysed only for Total Golodirsén group.

| | | | | |
|--------------------------------------|---------------------------------|--|--|--|
| End point values | Part 2a: Total Golodirsén Group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | 12.508 (± 14.6012) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2b: Percent Change From Baseline in Forced Vital Capacity Predicted (FVC%p) at Week144 in Untreated Group (Natural History of Non-exon 53)

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Part 2b: Percent Change From Baseline in Forced Vital Capacity Predicted (FVC%p) at Week144 in Untreated Group (Natural History of Non-exon 53) ^[17] |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

FVC is the total amount of air exhaled during the forced expiratory volume test that is measured during spirometry; and is the most important measurement of lung function. This test required subject to breath into a tube connected to a machine that measures the amount of air that can be moved in and out of the lungs after taking an inhaled bronchodilator medicine which is used to dilate subject's bronchial (breathing) tubes. Percent of predicted FVC = (observed value)/ (predicted value) * 100%. Efficacy set consisted of all randomised subjects from Part 1 and all Part 2 subjects who had at least 1 post-baseline functional assessment. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 144 | |

Notes:

[17] - 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: This endpoint was analysed only for Untreated Group (Natural History of Non-exon 53).

| | | | | |
|-----------------------------|-----------------------------------------------------------|--|--|--|
| End point values | Part 2b: Untreated Group (Natural History of Non-exon 53) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: percent change | | | | |

| | | | | |
|--------------------------------------|----------------------------|--|--|--|
| arithmetic mean (standard deviation) | -6.739 (\pm 17.5278) | | | |
|--------------------------------------|----------------------------|--|--|--|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 189 weeks

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Part 1: Placebo |
|-----------------------|-----------------|

Reporting group description:

Subjects received placebo-matched to golodirsen IV infusions, once weekly for up to 12 weeks in Part 1.

| | |
|-----------------------|------------------------------|
| Reporting group title | Part 1: Golodirsen (4 mg/kg) |
|-----------------------|------------------------------|

Reporting group description:

Subjects received golodirsen IV infusions, at dose level of 4 mg/kg, once weekly for 2 weeks in Part 1.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Part 1: Golodirsen (10 mg/kg) |
|-----------------------|-------------------------------|

Reporting group description:

Subjects received golodirsen IV infusions, at a dose level of 10 mg/kg, once weekly for the next 2 weeks (i.e., up to Week 4) in Part 1.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Part 1: Golodirsen (20 mg/kg) |
|-----------------------|-------------------------------|

Reporting group description:

Subjects received golodirsen IV infusions, at a dose level of 20 mg/kg, once weekly for the next 2 weeks (i.e., up to Week 6) in Part 1.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Part 1: Golodirsen (30 mg/kg) |
|-----------------------|-------------------------------|

Reporting group description:

Subjects received golodirsen IV infusions, at a dose level of 30 mg/kg, once weekly from Week 7 to Week 12 in Part 1.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Part 2a: Total Golodirsen Group |
|-----------------------|---------------------------------|

Reporting group description:

All subjects from Part 1 (who previously received placebo or golodirsen) and including additional new subjects received golodirsen 30 milligram (mg)/kilogram (kg) once weekly, for up to 168 weeks in Part 2. Dosing was interrupted or halted when any specific predefined stopping criteria was met or if warranted at the discretion of the Sponsor or Investigator.

| | |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Part 2b: Untreated Group (Natural History of Non-exon 53) |
|-----------------------|-----------------------------------------------------------|

Reporting group description:

Untreated subjects intended to evaluate the natural history of the disease with DMD and various genetic mutations (not amenable to exon 53 skipping) were included in this group and did not received any treatment. Subjects underwent the same study assessments as treated subjects in other reporting groups (except for pharmacokinetic [PK] sampling and muscle biopsies), but at a reduced schedule through Week 144. Thus, the untreated subjects are not considered a control group.

| Serious adverse events | Part 1: Placebo | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) |
|---------------------------------------------------|-----------------|------------------------------|-------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|------------------------------------------------------|---------------|---------------|---------------|
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| Gastrointestinal disorders | | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| Tooth development disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 | | | |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| Infections and infestations | | | |

| | | | |
|-------------------------------------------------|---------------|---------------|---------------|
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (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 |

| Serious adverse events | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) | Part 2a: Total Golodirsen Group |
|------------------------------------------------------|----------------------------------|----------------------------------|------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 4 / 25 (16.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth development disorder | | | |

| | | | |
|---------------------------------------------------|-----------------------------------------------------------|---------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (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 | | | |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (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 |
| Infections and infestations | | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serious adverse events | Part 2b: Untreated Group (Natural History of Non-exon 53) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|------------------------------------------------------|----------------|--|--|
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth development disorder | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Part 1: Placebo | Part 1: Golodirsen (4 mg/kg) | Part 1: Golodirsen (10 mg/kg) |
|---------------------------------------------------------------------|-----------------|------------------------------|-------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 5 / 8 (62.50%) | 5 / 8 (62.50%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemangioma of skin | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 8 (25.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 6 | 2 | 1 |
| Abasia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site bruise | | | |

| | | | |
|-------------------------------------------------|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Infusion site pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site related reaction | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |

| | | | |
|-----------------------------|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Choking | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stress | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aggression | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Panic attack | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| | | | |
|------------------------------------------------|----------------|---------------|---------------|
| Investigations | | | |
| Vitamin D decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count increased | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 12 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scratch | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back injury | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint injury | | | |

| | | | |
|--------------------------------------------------------------------------------------------|--------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Muscle strain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Spinal compression fracture subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Hand fracture subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 |
| Ventricular dysfunction subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---------------------------------------------------------------------------------------------|--------------------|---------------------|---------------------|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Rectal haemorrhage | | | |

| | | | |
|----------------------------------------|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Glossitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Tooth discolouration | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 3 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Petechiae subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 |
| Rash papular subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 3 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Infections and infestations Rhinitis subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 3 | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 3 | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 |
| Influenza | | | |

| | | | |
|-----------------------------------------|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Hordeolum | | | |

| | | | |
|------------------------------------|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Part 1: Golodirsen (20 mg/kg) | Part 1: Golodirsen (30 mg/kg) | Part 2a: Total Golodirsen Group |
|------------------------------------------------------------------------|----------------------------------|----------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 6 / 8 (75.00%) | 25 / 25 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Haemangioma of skin | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|------------------------|
| Haematoma subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Flushing subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 4 / 25 (16.00%) 5 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 4 / 8 (50.00%) 16 | 13 / 25 (52.00%) 33 |
| Abasia subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 4 / 25 (16.00%) 4 |
| Catheter site bruise subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 8 (12.50%) 2 | 3 / 25 (12.00%) 4 |
| Catheter site pain subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 | 3 / 25 (12.00%) 5 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 3 / 25 (12.00%) 7 |
| Infusion site pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 3 / 25 (12.00%) 4 |
| Gait disturbance subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Peripheral swelling | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Catheter site related reaction | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 8 (37.50%) | 16 / 25 (64.00%) |
| occurrences (all) | 0 | 12 | 57 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 8 (25.00%) | 12 / 25 (48.00%) |
| occurrences (all) | 0 | 6 | 43 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 6 / 25 (24.00%) |
| occurrences (all) | 0 | 2 | 11 |
| Choking | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 4 | 3 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Productive cough | | | |

| | | | |
|--------------------------------------------------|--------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 25 (8.00%) 3 |
| Psychiatric disorders | | | |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Stress | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Aggression | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Vitamin D decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 9 / 25 (36.00%) |
| occurrences (all) | 0 | 2 | 13 |
| Fall | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 6 / 25 (24.00%) |
| occurrences (all) | 0 | 0 | 18 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 6 / 25 (24.00%) |
| occurrences (all) | 0 | 0 | 7 |
| Scratch | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 6 / 25 (24.00%) |
| occurrences (all) | 0 | 0 | 9 |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 4 / 25 (16.00%) |
| occurrences (all) | 0 | 2 | 5 |
| Back injury | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 4 / 25 (16.00%) |
| occurrences (all) | 0 | 2 | 7 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 4 / 25 (16.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 4 / 25 (16.00%) |
| occurrences (all) | 0 | 0 | 5 |
| Head injury | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 2 | 4 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|-----------------------------------------------------------------------------|---------------------|----------------------|------------------------|
| Ventricular dysfunction subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 3 / 8 (37.50%) 12 | 11 / 25 (44.00%) 51 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 25 (8.00%) 3 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 8 (0.00%) 0 | 1 / 25 (4.00%) 3 |
| Syncope subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 3 / 25 (12.00%) 4 |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 8 (12.50%) 4 | 7 / 25 (28.00%) 21 |
| Eye disorders | | | |
| Eye pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 8 (12.50%) 2 | 2 / 25 (8.00%) 4 |
| Gastrointestinal disorders | | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 8 (12.50%) 2 | 15 / 25 (60.00%) 38 |
| Diarrhoea | | | |

| | | | |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 14 / 25 (56.00%) |
| occurrences (all) | 0 | 2 | 29 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 9 / 25 (36.00%) |
| occurrences (all) | 0 | 0 | 19 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 8 (25.00%) | 9 / 25 (36.00%) |
| occurrences (all) | 1 | 4 | 25 |
| Nausea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 5 / 25 (20.00%) |
| occurrences (all) | 0 | 0 | 10 |
| Constipation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 4 / 25 (16.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Toothache | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glossitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth discolouration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-------------------------------------------------|----------------|----------------|------------------|
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | 6 / 25 (24.00%) |
| occurrences (all) | 1 | 0 | 8 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 0 | 8 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Eczema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Erythema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 11 / 25 (44.00%) |
| occurrences (all) | 0 | 4 | 16 |

| | | | |
|-----------------------------------------|---------------|----------------|------------------|
| Back pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 8 (25.00%) | 10 / 25 (40.00%) |
| occurrences (all) | 0 | 4 | 38 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 9 / 25 (36.00%) |
| occurrences (all) | 0 | 2 | 26 |
| Infections and infestations | | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 8 (25.00%) | 16 / 25 (64.00%) |
| occurrences (all) | 0 | 4 | 31 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 13 / 25 (52.00%) |
| occurrences (all) | 0 | 2 | 39 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | 8 / 25 (32.00%) |
| occurrences (all) | 0 | 2 | 14 |
| Influenza | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 5 / 25 (20.00%) |
| occurrences (all) | 0 | 0 | 7 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 3 / 25 (12.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Oral herpes | | | |

| | | | |
|------------------------------------|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|------------------------------------------------------------------------|--------------------|--------------------|---------------------|
| Iron deficiency subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 8 (0.00%) 0 | 0 / 25 (0.00%) 0 |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--|--|
| Non-serious adverse events | Part 2b: Untreated Group (Natural History of Non-exon 53) | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 10 / 14 (71.43%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Haemangioma of skin subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Vascular disorders Haematoma subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Flushing subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | | |
| Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | | |
| Abasia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | | |
| Catheter site bruise | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infusion site pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site related reaction | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | | |
| occurrences (all) | 3 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Choking | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stress | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Panic attack | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|------------------------------------------------|----------------|--|--|
| Investigations | | | |
| Vitamin D decreased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scratch | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back injury | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Joint injury | | | |

| | | | |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---------------------------------------------------------------------------------------------|----------------------|--|--|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Constipation subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | | |
| Rectal haemorrhage | | | |

| | | | |
|----------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Glossitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tooth discolouration | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Petechiae</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash papular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 14 (0.00%)</p> <p>0</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>0 / 14 (0.00%)</p> <p>0</p> <p>0 / 14 (0.00%)</p> <p>0</p> | | |
| <p>Renal and urinary disorders</p> <p>Proteinuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 14 (0.00%)</p> <p>0</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 14 (0.00%)</p> <p>0</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>0 / 14 (0.00%)</p> <p>0</p> | | |
| <p>Infections and infestations</p> <p>Rhinitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p> | <p>0 / 14 (0.00%)</p> <p>0</p> <p>4 / 14 (28.57%)</p> <p>4</p> <p>0 / 14 (0.00%)</p> <p>0</p> | | |

| | | | |
|-----------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Otitis media | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | | |
| occurrences (all) | 2 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hordeolum | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Scarlet fever | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 August 2014 | Amendment 1: Added the occurrence of greater than or equal to (\geq) 2 severe AEs to the stopping rules. Added that if interruption of dosing was warranted at the discretion of Sarepta or Investigation, re-initiation of dosing was permitted, if deemed appropriate following safety data review by Sarepta. |
| 19 November 2014 | Amendment 2: Changed magnetic resonance imagings (MRIs) to optional at 12 weeks and 24 weeks for the untreated control group in Part 2. Removed the Week 36 leg muscle MRI for both treated and untreated groups in Part 2. Removed the untreated control group Part 2 Week 1 functional assessments for North Star Ambulatory Assessment (NSAA), 6MWT, pulmonary function tests, and the timed 4-step. Removed the assessment of vital signs for the untreated control group from Weeks 5 to 7, 9 to 11, 13 to 15, 17 to 19, 21 to 23, 25 to 35, and 37 to 47. Updated language for the untreated control group functional assessments in Study Assessments. Clarified that subjects in the untreated control group could have been enrolled concurrently in an observational study, unless it interfered with assessments in this study. Corrected the concentration of the human equivalent dose in Rationale for Initial Dose. |
| 07 April 2015 | Amendment 3: Changed the stopping rule regarding increases in serum creatinine to take into account the natural variability of serum creatinine levels observed in DMD subjects and to reflect the standard practice of requiring a confirmatory laboratory test for changes in test results. Reduced the frequency of assessments for the untreated control group in Part 2 of the study in order to reduce the burden on subjects and parents in this group. Separated the informed consent from the inclusion/exclusion criteria assessments. Removed the assessment of anti-PMO antibodies from the study. |
| 09 October 2015 | Amendment 4: Added an Extension Phase to Part 2, which extended the Part 2 treatment period by 96 weeks and defined the end of study as Week 148 (144 weeks of treatment and a follow-up safety visit 4 weeks after the last on-study dose). This included adding a schedule of assessments for the safety extension phase in Part 2. |

| | |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 April 2016 | <p>Amendment 5:</p> <p>Part 2 and the Part 2 Extension Phase, which was added in Amendment 4, were combined. In addition, the comparison period between treated subjects and untreated control subjects was extended from Week 48 (original end of Part 2) to Week 144 (end of Extension Phase of Part 2).</p> <p>Clarified that new subjects in Part 2 were treatment-naïve.</p> <p>Added specific information on requirements for muscle biopsies at Week 48.</p> <p>Clarified that modifications to dose based on weight was acceptable, provided the dose was equivalent.</p> <p>Removed RT-PCR as the methodology used to determine exon 53 skipping.</p> <p>Included immunogenicity in safety endpoints.</p> <p>Clarified strategy for interim review of safety and efficacy data by the DSMB.</p> <p>Changed that magnetic resonance scans were to be performed at Baseline and Week 12 of Part 1, not at Week 1.</p> <p>Added the collection of blood samples at Week 1 prior to the first infusion to provide a baseline for biomarkers and immunogenicity.</p> <p>Clarified that control subjects were to undergo all procedures at Screening and Baseline except for skin/muscle biopsies.</p> <p>Added Moviplate to Screening/Baseline assessments.</p> <p>Added language regarding an interim analysis and specified that safety data were to be reviewed in an ongoing basis by the DSMB.</p> |
| 20 October 2016 | <p>Amendment 6:</p> <p>Removed actimetry as an endpoint due to problems with the measurement device (ActiMyo).</p> |
| 21 April 2017 | <p>Amendment 7:</p> <p>Added text to distinguish the difference between efficacy and biological (ie, pharmacodynamics) endpoints.</p> <p>Switched the primary biological endpoint (percentage of dystrophin-positive fibers) with a secondary biological endpoint (dystrophin protein levels by Western blot).</p> |
| 08 November 2017 | <p>Amendment 8:</p> <p>Extended the treatment period for golodirsen-treated subjects from 144 weeks to 168 weeks, thereby also extending the total study duration for golodirsen-treated subjects from 166 weeks to 190 weeks.</p> <p>Added the option of actimetry assessment at Week 144 (± 2 weeks) using a newly available version of the ActiMyo device.</p> <p>Specified that forced vital capacity% was the key respiratory function endpoint.</p> <p>Added an interim analysis to permit muscle biopsy analysis after the last biopsy was collected (i.e, after all golodirsen-treated subjects from Part 1 and Part 2 had completed the Week 48 muscle biopsy in Part 2).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported