# Clinical trial results:
# An Open-Label, Multi-Center, Study With a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy

## Summary

| | |
|---|---|
| EudraCT number | 2016-005002-19 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 14 June 2019 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 16 January 2021 |
| First version publication date | 28 June 2020 |
| Version creation reason | • New data added to full data set<br>Need to additional data for secondary endpoint |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 4658-301 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02255552 |
| 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) | EMEA-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 | 04 March 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the effect of eteplirsen (AVI-4658) on ambulation, endurance, and muscle function as measured by change from Baseline to 96 weeks in the 6 minute walk test (6MWT) as compared to an untreated control arm of Duchenne muscular dystrophy (DMD) subjects amenable to skipping exon 51.

Protection of trial subjects:

Written informed consent from each subject or subjects 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 | 01 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 109 |
| Worldwide total number of subjects | 109 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 96 |
| Adolescents (12-17 years) | 13 |

| | |
|---|---|
| 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 40 sites in the United States.

### Pre-assignment

Screening details:

A total of 109 subjects were enrolled in the study. Only 79 subjects were treated and the remaining subjects were not applicable for treatment as those subjects assessed under "Untreated" arm.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Eteplirsen 30 mg/kg |

Arm description:

Subjects with genotypically confirmed Duchenne muscular dystrophy (DMD) with genetic deletions amenable to treatment by exon 51 skipping received Eteplirsen as an Intravenous (IV) infusion, at a dose of 30 milligram per kilogram (mg/kg) once weekly for 96 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Eteplirsen |
| Investigational medicinal product code | |
| Other name | EXONDYS 51® |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received eteplirsen 30 mg/kg IV infusion once weekly.

| | |
|---|---|
| **Arm title** | Untreated Control Group (non-exon 51 amenable subjects) |

Arm description:

DMD subjects with mutations amenable to skipping of any exon(s) except exon 51 did not receive any treatment, but completed study assessments up to 96 weeks.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) |
|---|---|---|
| Started | 79 | 30 |
| Completed | 78 | 15 |
| Not completed | 1 | 15 |
| Consent withdrawn by subject | 1 | 4 |
| Subjects enrolled into another study | - | 11 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Eteplirsen 30 mg/kg |
| Reporting group description: | |
| Subjects with genotypically confirmed Duchenne muscular dystrophy (DMD) with genetic deletions amenable to treatment by exon 51 skipping received Eteplirsen as an Intravenous (IV) infusion, at a dose of 30 milligram per kilogram (mg/kg) once weekly for 96 weeks. | |
| Reporting group title | Untreated Control Group (non-exon 51 amenable subjects) |
| Reporting group description: | |
| DMD subjects with mutations amenable to skipping of any exon(s) except exon 51 did not receive any treatment, but completed study assessments up to 96 weeks. | |

| Reporting group values | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | Total |
|---|---|---|---|
| Number of subjects | 79 | 30 | 109 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 9.1 | 8.8 | |
| standard deviation | ± 2.04 | ± 1.76 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 79 | 30 | 109 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 5 | 1 | 6 |
| Black | 2 | 0 | 2 |
| Native Hawaiian or Other Pacific Islander | 2 | 0 | 2 |
| White | 67 | 26 | 93 |
| Other | 3 | 3 | 6 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 7 | 6 | 13 |
| Not Hispanic or Latino | 71 | 24 | 95 |
| Not Reported | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Unknown | 1 | 0 | 1 |

## End points

### End points reporting groups

| Reporting group title | Eteplirsen 30 mg/kg |
|---|---|

Reporting group description:

Subjects with genotypically confirmed Duchenne muscular dystrophy (DMD) with genetic deletions amenable to treatment by exon 51 skipping received Eteplirsen as an Intravenous (IV) infusion, at a dose of 30 milligram per kilogram (mg/kg) once weekly for 96 weeks.

| Reporting group title | Untreated Control Group (non-exon 51 amenable subjects) |
|---|---|

Reporting group description:

DMD subjects with mutations amenable to skipping of any exon(s) except exon 51 did not receive any treatment, but completed study assessments up to 96 weeks.

### Primary: Change From Baseline in the 6 Minute Walk Test (6MWT) Distance at Week 96

| End point title | Change From Baseline in the 6 Minute Walk Test (6MWT) Distance at Week 96[1] |
|---|---|

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 96 was reported. Primary efficacy set consisted of all subjects in the efficacy set (all subjects in eteplirsen-treated and untreated control groups who had at least 1 post-baseline functional assessment) who had a Baseline 6MWT distance of 300 to 450 meters, inclusive. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 96

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: Comparisons between the eteplirsen-treated group and the untreated control group were not to be performed due to the small number of subjects in the untreated control group (small population size and large dropout rate) and the differences in the populations between the treated and untreated groups. Instead only descriptive summaries were to be presented.

| **End point values** | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 9 | | |
| Units: meters | | | | |
| arithmetic mean (standard deviation) | -117.91 (± 128.488) | -133.56 (± 129.333) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Dystrophin Protein Levels Determined by Western Blot at Week 96

| End point title | Change From Baseline in Dystrophin Protein Levels Determined by Western Blot at Week 96[2] |
|---|---|

End point description:

Change from baseline in dystrophin protein levels (in muscle biopsy samples) were determined by Western blot. For each time point, 2 blocks of tissues were analyzed by Western blot, each with 2 replicates of gels to determine the dystrophin level as compared to a healthy individual (Percent Normal). The block average value from 2 replicate gels was computed. The overall average was calculated as the mean of the block average values. The overall average values were used for all analyses. In case only 1 gel was available for a block, then that value was used as the block average value. Analysis Set consisted of a subset of subjects who received at least 1 dose of eteplirsen and had both baseline and 1 post-dose muscle biopsy samples evaluable for dystrophin expression at Week 96. 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 the Untreated Control group.

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

End point timeframe:

Baseline, Week 96

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was not planned to be collected and analysed for Untreated Control group.

| **End point values** | Eteplirsen 30 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Percent Normal Dystrophin Protein Level | | | | |
| arithmetic mean (standard deviation) | 0.516 (± 0.7236) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Having Ability to Rise Independently From the Floor Determined Based on North Star Ambulatory Assessment (NSAA) at Week 96

| End point title | Number of Subjects Having Ability to Rise Independently From the Floor Determined Based on North Star Ambulatory Assessment (NSAA) at Week 96 |
|---|---|

End point description:

NSAA is a clinician-administered scale that rates subject performance on 17-items and included assessments of abilities such as 10-meter walk/run, rising from a sit to stand, standing on 1 leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. For all activities, subjects were graded as follows: 0 = unable to achieve goal independently; 1 = modified method but achieves goal independent of physical assistance from another and 2 = normal, no obvious modification of activity. Number of Subjects having ability to rise independently from the floor indicated by a NSAA Rise from floor sub score greater than 0 (unable to achieve goal independently) was reported. Primary Efficacy Set was analysed. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint.

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

End point timeframe:

Week 96

| End point values | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 9 | | |
| Units: Subjects | 33 | 3 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects who Lost Ambulation (LOA) by Week 96

| End point title | Number of Subjects who Lost Ambulation (LOA) by Week 96 |
|---|---|

End point description:

Number of subjects who lost ambulation (LOA) by Week 96 was reported. Subject were considered non-ambulatory if each of the 3 conditions below were met: NSAA walk subscore was "0" (unable to achieve goal independently) on 2 consecutive days within a visit or NSAA was not done due to reason related to non-ambulation; 6MWT was not done with any reason related to permanent non-ambulation; and no later data showing this subject was still ambulatory. This was not required if non ambulatory status occurred at the time of early withdrawal or at the end of Week 96 assessment. NSAA is a 17-item scale to assess the subjects abilities; total score range from 0 (if all the activities are failed) to 34 (if all the activities are achieved) with higher scores indicating better performance on the assessment/ fully-independent function. Primary efficacy set was analysed.

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

End point timeframe:

Up to Week 96

| End point values | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 | 20 | | |
| Units: Subjects | 12 | 1 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Forced Vital Capacity Percent (FVC%) Predicted at Weeks 96

| End point title | Change From Baseline in Forced Vital Capacity Percent (FVC%) |
|---|---|

| | |
|---|---|
| | Predicted at Weeks 96 |

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 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 is used to dilate subject's bronchial (breathing) tubes. Percent of predicted FVC = (observed value) / (predicted value) * 100%. Primary efficacy set consisted of all subjects in the efficacy set (all subjects in eteplirsen-treated and untreated control groups who had at least 1 post-baseline functional assessment) who had a Baseline 6MWT distance of 300 to 450 meters, inclusive. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 96

| **End point values** | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 9 | | |
| Units: Percentage of predicted FVC | | | | |
| arithmetic mean (standard deviation) | -3.413 (± 12.4011) | -2.461 (± 9.6000) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in North Star Ambulatory Assessment (NSAA) Total Scores at Week 96

| | |
|---|---|
| End point title | Change From Baseline in North Star Ambulatory Assessment (NSAA) Total Scores at Week 96 |

End point description:

NSAA is a clinician-administered scale that rates subject performance on 17-items and included assessments of abilities such as 10-meter walk/run, rising from a sit to stand, standing on 1 leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. Subjects were graded as follows: 0 = unable to achieve goal independently; 1 = modified method but achieves goal independent of physical assistance from another and 2 = normal, no obvious modification of activity. NSAA total score was derived by summing the scores for all the individual items and range from 0 (if all the activities are failed) to 34 (if all the activities are achieved) with higher scores indicating better performance on the assessment/ fully-independent function. Primary Efficacy Set was analysed. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 96

| End point values | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 9 | | |
| Units: unit on scale | | | | |
| arithmetic mean (standard deviation) | -7.23 (± 5.173) | -8.44 (± 9.812) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Dystrophin Intensity Levels Determined by Immunohistochemistry (IHC) at Week 96

| End point title | Change From Baseline in Dystrophin Intensity Levels Determined by Immunohistochemistry (IHC) at Week 96[3] |
|---|---|

End point description:

Change from baseline in dystrophin intensity levels (in muscle biopsy samples) was determined by Immunohistochemistry. Analysis Set consisted of a subset of participants who received at least 1 dose of eteplirsen and had both baseline and 1 post-dose muscle biopsy samples evaluable for dystrophin expression at Week 96. Here, "Number of Subjects Analyzed" signifies number of subjects who were evaluable for this endpoint. Data for this endpoint was not planned to be collected and analyzed for the Untreated Control group.

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

End point timeframe:

Baseline, Week 96

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Untreated Control group.

| End point values | Eteplirsen 30 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Percent dystrophin positive fibers | | | | |
| arithmetic mean (standard deviation) | 0.030 (± 0.0360) | | | |

### 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 to Week 144.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Eteplirsen 30 mg/kg |

Reporting group description:

Subjects with genotypically confirmed Duchenne muscular dystrophy (DMD) with genetic deletions amenable to treatment by exon 51 skipping received Eteplirsen as an Intravenous (IV) infusion, at a dose of 30 milligram per kilogram (mg/kg) once weekly for 96 weeks.

| | |
|---|---|
| Reporting group title | Untreated Control Group (non-exon 51 amenable subjects) |

Reporting group description:

DMD subjects with mutations amenable to skipping of any exon(s) except exon 51 did not receive any treatment, but completed study assessments up to 96 weeks.

| Serious adverse events | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 79 (13.92%) | 2 / 30 (6.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis chemical | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abasia | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenitis viral | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Eteplirsen 30 mg/kg | Untreated Control Group (non-exon 51 amenable subjects) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 78 / 79 (98.73%) | 24 / 30 (80.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 5 | 1 | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 20 / 79 (25.32%) | 1 / 30 (3.33%) | |
| occurrences (all) | 28 | 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 0 / 30 (0.00%) | |
| occurrences (all) | 14 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Catheter site pain | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 0 / 30 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Infusion site bruising | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Infusion site pain | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 14 / 79 (17.72%) | 0 / 30 (0.00%) | |
| occurrences (all) | 23 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 36 / 79 (45.57%) | 1 / 30 (3.33%) | |
| occurrences (all) | 77 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 25 / 79 (31.65%) | 1 / 30 (3.33%) | |
| occurrences (all) | 46 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 22 / 79 (27.85%) | 0 / 30 (0.00%) | |
| occurrences (all) | 36 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 20 / 79 (25.32%) | 0 / 30 (0.00%) | |
| occurrences (all) | 33 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 11 / 79 (13.92%) | 1 / 30 (3.33%) | |
| occurrences (all) | 16 | 2 | |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 0 / 30 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Upper respiratory tract congestion | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 1 / 30 (3.33%) | |
| occurrences (all) | 8 | 1 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Anxiety | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 30 (3.33%) | |
| occurrences (all) | 7 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 25 / 79 (31.65%) | 0 / 30 (0.00%) | |
| occurrences (all) | 34 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 24 / 79 (30.38%) | 1 / 30 (3.33%) | |
| occurrences (all) | 56 | 2 | |
| Fall | | | |
| subjects affected / exposed | 22 / 79 (27.85%) | 6 / 30 (20.00%) | |
| occurrences (all) | 72 | 10 | |
| Skin abrasion | | | |
| subjects affected / exposed | 21 / 79 (26.58%) | 0 / 30 (0.00%) | |
| occurrences (all) | 60 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 12 / 79 (15.19%) | 3 / 30 (10.00%) | |
| occurrences (all) | 18 | 5 | |
| Arthropod bite | | | |
| subjects affected / exposed | 10 / 79 (12.66%) | 1 / 30 (3.33%) | |
| occurrences (all) | 14 | 1 | |
| Muscle strain | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 0 / 30 (0.00%) | |
| occurrences (all) | 14 | 0 | |
| Laceration | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 1 / 30 (3.33%) | |
| occurrences (all) | 4 | 1 | |
| Limb injury | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Spinal compression fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Torus fracture | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 40 / 79 (50.63%) | 1 / 30 (3.33%) | |
| occurrences (all) | 155 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 0 / 30 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 39 / 79 (49.37%) | 0 / 30 (0.00%) | |
| occurrences (all) | 82 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 20 / 79 (25.32%) | 1 / 30 (3.33%) | |
| occurrences (all) | 47 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 17 / 79 (21.52%) | 0 / 30 (0.00%) | |
| occurrences (all) | 31 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 14 / 79 (17.72%) | 3 / 30 (10.00%) | |
| occurrences (all) | 23 | 4 | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 79 (10.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 5 | 1 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 1 / 30 (3.33%) | |
| occurrences (all) | 4 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 17 / 79 (21.52%) | 2 / 30 (6.67%) | |
| occurrences (all) | 23 | 2 | |
| Erythema | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 0 / 30 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 29 / 79 (36.71%) | 1 / 30 (3.33%) | |
| occurrences (all) | 53 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 26 / 79 (32.91%) | 2 / 30 (6.67%) | |
| occurrences (all) | 51 | 3 | |
| Arthralgia | | | |
| subjects affected / exposed | 16 / 79 (20.25%) | 2 / 30 (6.67%) | |
| occurrences (all) | 28 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 0 / 30 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 30 (3.33%) | |
| occurrences (all) | 10 | 1 | |
| Musculoskeletal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 79 (7.59%) | 0 / 30 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 2 / 30 (6.67%) | |
| occurrences (all) | 15 | 2 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 29 / 79 (36.71%) | 3 / 30 (10.00%) | |
| occurrences (all) | 52 | 3 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 25 / 79 (31.65%) | 1 / 30 (3.33%) | |
| occurrences (all) | 39 | 1 | |
| Ear infection | | | |
| subjects affected / exposed | 11 / 79 (13.92%) | 0 / 30 (0.00%) | |
| occurrences (all) | 16 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 1 / 30 (3.33%) | |
| occurrences (all) | 10 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 1 / 30 (3.33%) | |
| occurrences (all) | 9 | 1 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 0 / 30 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 30 (3.33%) | |
| occurrences (all) | 8 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 30 (3.33%) | |
| occurrences (all) | 9 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 May 2014 | The definition for stable pulmonary function (FVC%p > 50% and not require nocturnal ventilation) was corrected in the inclusion criteria.<br>The biomarkers to be assessed were specified: micro-ribonucleic acid and matrix metalloprotein-9.<br>The exclusion criteria were clarified to note that concurrent enrollment in any clinical study (including observational studies) was not permitted.<br>Urine cystatin C was removed from the schedule of events. |
| 22 July 2015 | The length of the study was expanded to collect additional longitudinal safety data as well as assess clinical and functional status over time. This amendment extended the treatment period from Week 48 to Week 96 and defined the end-of-study as Week 100. |
| 15 July 2016 | The study duration was lengthened from 48 weeks to 96 weeks; this period was no longer considered an extension period.<br>A Safety Extension Period was added for eteplirsen-treated subjects only (not to exceed 48 weeks) until the product was commercially available or until they could transition into a separate eteplirsen study.<br>The secondary objectives and additional efficacy objectives were adjusted to prioritize those likely to show change after 96 weeks.<br>The primary efficacy endpoint was changed to Week 96 and the language for the primary, secondary, and additional efficacy endpoints was adjusted based on the revised study objectives.<br>More flexibility was allowed in the use of untreated control subjects, if < 80% of the planned control subjects were enrolled. The control group may have been augmented with external control subjects, including those that may have been amenable to exon 51 skipping.<br>More flexibility was allowed regarding previous treatment with drisapersen. Subjects may have been eligible if they discontinued drisapersen at least 3 months prior to screening, provided they were free of symptoms related to drisapersen treatment.<br>Additional PK (serial) sampling times were added to Weeks 48 and 96, and predose and postdose (sparse) sampling times were adjusted for other visits at which PK sampling was performed.<br>The timing of postbaseline biopsy samples was clarified. Biopsies must have occurred within 2 weeks after the specified visit, after the clinical evaluation, and at least 48 hours after the most recent infusion.<br>Schedule of events was revised to eliminate the Week 100 visit for both eteplirsen treated and untreated subjects and clarify that infusions were to continue weekly (by adding Week 49 to the table) for eteplirsen-treated subjects.<br>An additional schedule of events and text for the Safety Extension were included for eteplirsen-treated subjects.<br>The statistical analysis sections for the revised endpoint analyses were revised. |
| 02 June 2017 | Target enrollment numbers were adjusted from 160 (80 for the eteplirsen-treated group and 80 for the untreated group) to 110 and the rationale for the sample size modified (including adjusting the power).<br>Timing of when in-home study drug infusion could have started was changed from Week 52 to Week 25. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/31237898