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 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 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 Units: years			
arithmetic mean	9.1	8.8	
standard deviation	± 2.04	± 1.76	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	79	30	109
Race 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 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. The biomarkers to be assessed were specified: micro-ribonucleic acid and matrix metalloprotein-9. The exclusion criteria were clarified to note that concurrent enrollment in any clinical study (including observational studies) was not permitted. 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. 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. The secondary objectives and additional efficacy objectives were adjusted to prioritize those likely to show change after 96 weeks. 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. 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. 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. 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. 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. 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. An additional schedule of events and text for the Safety Extension were included for eteplirsen-treated subjects. 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). 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