Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability, and Pharmacokinetics Study of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, Administered Over 28 Weeks in the Treatment of Ambulant Subjects with Duchenne Muscular Dystrophy

Summary

EudraCT number	2016-005000-26
Trial protocol	Outside EU/EEA
Global end of trial date	29 February 2012

Results information

Result version number	v2 (current)
This version publication date	01 August 2019
First version publication date	28 March 2019
Version creation reason	• Correction of full data set Update to Sponsor phone number

Trial information

Trial identification

Sponsor protocol code	4658-us-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01396239
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sarepta Therapeutics, Inc.
Sponsor organisation address	215 First St., Cambridge, United States, MA 02142
Public contact	Medical Director, Sarepta Therapeutics, Inc., +1 888-727-3782, clinicaltrials@sarepta.com
Scientific contact	Medical Director, Sarepta Therapeutics, Inc., +1 888-727-3782, 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	01 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 February 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of AVI-4658 (eteplirsen) at 50 and 30 mg/kg/week (wk) doses in subjects diagnosed with Duchenne muscular dystrophy (DMD).

Protection of trial subjects:

Written informed consent from each patient or patient's parent(s) or legal guardian(s), if applicable, and written assent from each patient, if applicable, were obtained before any study-specific screening or baseline period evaluations were performed. The anonymity of participating patients 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	18 July 2011
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: 12
Worldwide total number of subjects	12
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)	12

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at single center in the United States from 18 July 2011 to 10 August 2011.

Period 1

Period 1 title	24 Weeks Blinded (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	AVI-4658 (Eteplirsen) 30 mg/kg

Arm description:

30 milligram per kilogram (mg/kg) eteplirsen for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	AVI-4658
Investigational medicinal product code	
Other name	Eteplirsen
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/kg eteplirsen once weekly for 24 weeks via a 60-minute IV infusion.

Arm title	AVI-4658 (Eteplirsen) 50 mg/kg

Arm description:

50 milligram per kilogram (mg/kg) eteplirsen for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	AVI-4658
Investigational medicinal product code	
Other name	Eteplirsen
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/kg eteplirsen once weekly for 24 weeks via a 60-minute IV infusion.

Arm title	Placebo

Arm description:

Placebo: phosphate buffered saline solution identical in appearance to eteplirsen for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo matched to AVI-4658 once weekly for 24 weeks via a 60-minute IV infusion.

Number of subjects in period 1	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo
Started	4	4	4
Completed	4	4	4

Baseline characteristics

Reporting groups	
Reporting group title	AVI-4658 (Eteplirsen) 30 mg/kg
Reporting group description:	
30 milligram per kilogram (mg/kg) eteplirsen for 24 weeks.	
Reporting group title	AVI-4658 (Eteplirsen) 50 mg/kg
Reporting group description:	
50 milligram per kilogram (mg/kg) eteplirsen for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo: phosphate buffered saline solution identical in appearance to eteplirsen for 24 weeks.	

Reporting group values	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo
Number of subjects	4	4	4
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 9.3 ± 0.5	 8.5 ± 1.29	 8.5 ± 1.73
Gender categorical Units: Subjects			
Female	0	0	0
Male	4	4	4

Reporting group values	Total		
Number of subjects	12		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -	 	
Gender categorical Units: Subjects			
Female	0		
Male	12		

End points

End points reporting groups

Reporting group title	AVI-4658 (Eteplirsen) 30 mg/kg
Reporting group description:	
30 milligram per kilogram (mg/kg) eteplirsen for 24 weeks.	
Reporting group title	AVI-4658 (Eteplirsen) 50 mg/kg
Reporting group description:	
50 milligram per kilogram (mg/kg) eteplirsen for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo: phosphate buffered saline solution identical in appearance to eteplirsen for 24 weeks.	
Subject analysis set title	Placebo - Week 12 Biopsy
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo - Biopsied after 12 weeks of dosing.	
Subject analysis set title	Placebo - Week 24 Biopsy
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo: Biopsied after 24 weeks of dosing.	

Primary: Change From Baseline in the Percentage (%) of Dystrophin Positive Fibers

End point title	Change From Baseline in the Percentage (%) of Dystrophin Positive Fibers[1][2]

End point description:

The primary efficacy end point was based on the pre-treatment and post-treatment change in the percentage (%) of dystrophin-positive fibers as measured in the muscle biopsy tissue on immunohistochemistry (IHC). The sample size for the study was selected based on the Proof of Principle approach.

End point type	Primary

End point timeframe:

After 12 weeks for 4 subjects who received 50 mg/kg and 2 subjects who received placebo. After 24 weeks for 4 subjects who received 30 mg/kg and 2 subjects who received placebo.

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: Only descriptive data was planned to be reported for this endpoint.

[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: Only arms applicable for this endpoint are reported.

End point values	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo - Week 12 Biopsy	Placebo - Week 24 Biopsy
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	4	4	2	2
Units: Percentage of dystrophin Pos. fibers				
least squares mean (full range (min-max))	23 (15.9 to 29.0)	0.79 (-9.3 to 7.4)	-0.63 (-5.8 to 4.5)	-7.48 (-8.5 to -6.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline: 6 Minute Walk Test (6MWT) - Intent to Treat Population (ITT)

End point title	Change From Baseline: 6 Minute Walk Test (6MWT) - Intent to Treat Population (ITT)

End point description:

Secondary end points was based on the pre-treatment and post-treatment Change from baseline: 6 Minute Walk Test (6MWT) - Intent to Treat population (ITT).

End point type	Secondary

End point timeframe:

24 weeks

End point values	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: Meters				
arithmetic mean (standard error)	-134.8 (± 72.36)	-2.3 (± 14.95)	-17.3 (± 14.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline: 6 Minute Walk Test (6MWT) - Modified Intent to Treat Population (mITT)

End point title	Change From Baseline: 6 Minute Walk Test (6MWT) - Modified Intent to Treat Population (mITT)

End point description:

Secondary end points was based on the pre-treatment and post-treatment of the 6MWT distance. Change from baseline: 6MWT - modified Intent-to-Treat population (mITT). The mITT population excludes 2 subjects in the 30 mg/kg arm who showed rapid disease progression within weeks of enrollment, and were unable to complete assessments that required ambulation at or beyond Week 24.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	4	
Units: Meters				
arithmetic mean (standard error)	-12.5 (± 1.50)	-2.3 (± 14.95)	-17.3 (± 14.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Hoc: Adverse Events >30%

End point title	Post-Hoc: Adverse Events >30%

End point description:

Adverse events that occurred in >30% of the overall subject population across treatment arms. Safety Population included all randomized subjects who received any amount of study drug. Analyses performed on the safety population were done according to the treatment actually received.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects				
Procedural Pain	1	3	3	
Oropharyngeal Pain	3	0	3	
Hypokalemia (a known side effect of steroids)	2	2	2	
Cough	1	1	2	
Extremity Pain	0	1	3	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Post-Hoc: Frequency of AEs Related to Eteplirsen

End point title	Post-Hoc: Frequency of AEs Related to Eteplirsen

End point description:

Frequency of AEs that the study physician considered to be any of the following: Related; Possibly related; or Probably related to eteplirsen. Safety Population included all randomized subjects who received any amount of study drug. Analyses performed on the safety population were done according to the treatment actually received.

End point type	Post-hoc

End point timeframe:

24 Weeks

End point values	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: Number of subjects				
Intermittent Nausea (mild)	0	0	1	
Other AEs related to eteplirsen	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0
Reporting groups	
Reporting group title	AVI-4658 (Eteplirsen) 30 mg/kg
Reporting group description: 30 milligram per kilogram (mg/kg) eteplirsen once weekly for 24 weeks via a 60-minute IV infusion.	
Reporting group title	AVI-4658 (Eteplirsen) 50 mg/kg
Reporting group description: 50 milligram per kilogram (mg/kg) eteplirsen once weekly for 24 weeks via a 60-minute IV infusion.	
Reporting group title	Placebo
Reporting group description: Placebo: phosphate buffered saline solution identical in appearance to eteplirsen for 24 weeks.	

Serious adverse events	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	AVI-4658 (Eteplirsen) 30 mg/kg	AVI-4658 (Eteplirsen) 50 mg/kg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
General disorders and administration site conditions			

Injection site pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	1	1	5
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
Oropharyngeal pain			
subjects affected / exposed	3 / 4 (75.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	4	0	4
Sinus congestion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract congestion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Back injury			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Foot fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Incision site pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Joint injury			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 4 (25.00%)	3 / 4 (75.00%)	3 / 4 (75.00%)
occurrences (all)	1	3	3
Wound dehiscence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	3
Somnolence			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Motion sickness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Petechiae			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urticaria thermal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
Bone pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	3 / 4 (75.00%)
occurrences (all)	0	2	3
Infections and infestations			
Enterobiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Soft tissue infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	2	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2011	Version 2 (Amendment 1) * Changed the dosing regimen from 50 or 100 mg/kg/wk eteplirsen administered for 12 weeks to 30 or 50 mg/kg/wk administered for 24 weeks. * Changed the overall duration of the study from 30 to 28 weeks. * Changed the design of the study from a dose escalation study to a randomized, double-blind, placebo-controlled, multiple-dose, efficacy, safety, tolerability, and PK study. * Changed the number of subjects from 5 subjects each in 4 groups to 4 subjects each in 3 groups (30 mg/kg/wk, 50 mg/kg/wk, and placebo), i.e., from an N of 20 to an N of 12 * Changed the age range for subject enrollment from 5 to 15 years of age to 7 to 13 years of age. * Added the requirement that subjects be able to walk between 200 and 350 meters on the 6MWT to the entry criteria. * Changed the entry requirement that subjects be on a stable dose of corticosteroids for at least 12 weeks before study entry to at least 24 weeks before study entry. * Added the requirement that the QTc interval at study entry not exceed 450 millisecond to the entry criteria. * Changed the infusion of study medication from "60 minutes for an IV infusion or 2 minutes for an IV bolus" to an IV infusion duration of 30 minutes. * Increased the frequency of laboratory assessments. * Modified the timing and frequency of PK sample collection. * Added post-treatment muscle biopsies to the list of required assessments. * Specified that the primary efficacy end point would be dystrophin production.
25 May 2011	Version 3 (Amendment 2) * Changed the infusion time from 30 to 60 minutes. * Condensed the Screening assessments into 1 visit (Visit 1) to be performed within 4 weeks of week 1: day 1. * Added the Timed 4-Step Test to the efficacy assessments. * Expanded the maximum distance on the 6MWT inclusion criterion from 350 to 400 meters. * Changed the Week 24 brief physical examination to a full physical examination.
22 June 2011	Version 4.0 (Amendment 3) * Clarified the frequency of urine collection for assessment of cystatin C. * Added urine kidney injury molecule -1 (KIM-1) analysis to the list of safety laboratory assessments.

10 August 2011	Version 5.0 (Amendment 4) * Clarified that the 6MWT would be administered twice during the Screening visit and that the mean of the 2 assessments ± 10% of the lower or upper limit (200 m, 400 m) would be the value used to determine qualification. * Specified that the Screening Holter monitor recording would be reviewed prior to the subject undergoing a muscle biopsy, and that if the average heart rate during the recording exceeded 100 beats per minute (bpm), the subject would either be started on β-blockers and rescreened in 4 weeks or excluded from the study. * Increased the clinically significant range on 24-hour Holter monitoring from 100 to greater than equal to >= 110 bpm and symptomatic. * Added collection of serum cystatin C to the list of safety laboratory assessments.
08 September 2011	Version 6.0 (Amendment 5) * Clarified that maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) would be measured, not % predicted MIP and MEP. * Clarified that vital signs would not be collected 4 hours after dosing if subject had been allowed to leave the site prior to that time. * Deleted the 24-hour total urine protein collection from the protocol, because the results from the initial collection were confounded by the presence of nitrogen in eteplirsen.
04 November 2011	Version 7.0 (Amendment 6) * Removed pulmonary function test (PFT) from the list of safety assessments as it was already included in the list of efficacy assessments. * Made the 6MWT a secondary end point. * Modified the statistical method to the Wilcoxon rank-sum test, because it was more appropriate for the sample size of this study. * Permitted subjects to be released 1 hour after completion of the study drug infusion after the first 4 doses at the discretion of the Principal Investigator if there were no infusion site reactions or other events associated with drug administration. * Removed peak inspiratory and expiratory flow from the list of PFT assessments, because these tests are measures for pulmonary obstruction, not intercostal or diaphragmatic muscle function. * The Extended upper limit of the window for the muscle biopsy was extended to 96 hours post dosing to allow the same surgeon to perform all biopsies. * Updated planned statistical analyses. * Removed the "mITT" and "per protocol" populations from the list of analysis populations and added a "full analysis population", which, like the safety population, included all subjects who received any study medication.
07 January 2012	Version 8.0 (Amendment 7) * Extended the duration of the study from 24 to 28 weeks. * Specified that beginning Week 25, subjects who received placebo for the first 24 weeks of the study would begin receiving the same dose of eteplirsen to which they were placebo-matched while those who received 50 or 30 mg/kg/wk eteplirsen for the first 24 weeks would continue to receive the same dose regimen of eteplirsen without interruption. * Specified that treatment assignment during the first 24 weeks of the study (eteplirsen vs. placebo) would remain blinded until the study was completed and the database had been locked. * Provided a schedule of assessments and guidance on the administration of study medication for Weeks 25 to 28.

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/23907995

http://www.ncbi.nlm.nih.gov/pubmed/26573217