



## Clinical trial results:

### Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201

#### Summary

EudraCT number	2016-005001-39
Trial protocol	Outside EU/EEA
Global end of trial date	16 August 2017

#### Results information

Result version number	v1 (current)
This version publication date	08 September 2019
First version publication date	08 September 2019

#### Trial information

##### Trial identification

Sponsor protocol code	4658-us-202
-----------------------	-------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01540409
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Sarepta Therapeutics Inc.
Sponsor organisation address	215 First Street, 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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 August 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy, safety, and tolerability of treatment with eteplirsen in Duchenne muscular dystrophy (DMD) subjects who have successfully completed Study 4658-us-201.

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	27 February 2012
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:

The study was conducted at 12 centers in the United States. Overall, 12 subjects who completed parent study 4658-us-201 (NCT01396239) were enrolled between July 2011 and February 2012 in this extension study (4658-us-202; NCT01540409). A 4-week open label period (Week 24-28) was observed between the parent and extension study.

### Pre-assignment

Screening details:

Subjects who received placebo in 4658-us-201 study were randomized in 1:1 ratio in this extension study to receive either eteplirsen 30 or 50 milligram per kilogram (mg/kg) and, those who received eteplirsen 30 or 50 mg/kg in 4658-us-201 received same treatment in this extension study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Eteplirsen 30 mg/kg

Arm description:

Subjects who received 30 mg/kg eteplirsen or placebo once weekly, intravenous (IV) infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 30 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.

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

Dosage and administration details:

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

<b>Arm title</b>	Eteplirsen 50 mg/kg
------------------	---------------------

Arm description:

Subjects who received 50 mg/kg eteplirsen or placebo once weekly, IV infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 50 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.

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

Dosage and administration details:

Subjects received 50 mg/kg eteplirsen IV infusion once weekly.

<b>Number of subjects in period 1</b>	Eteplirsen 30 mg/kg	Eteplirsen 50 mg/kg
Started	6	6
Completed	6	6

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Subjects who received 30 mg/kg eteplirsen or placebo once weekly, intravenous (IV) infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 30 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.

Reporting group title	Eteplirsen 50 mg/kg
-----------------------	---------------------

Reporting group description:

Subjects who received 50 mg/kg eteplirsen or placebo once weekly, IV infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 50 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.

Reporting group values	Eteplirsen 30 mg/kg	Eteplirsen 50 mg/kg	Total
Number of subjects	6	6	12
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	9.2 ± 0.75	8.8 ± 1.47	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	6	6	12
Region of Enrollment Units: Subjects			
United States	6	6	12

## End points

### End points reporting groups

Reporting group title	Eteplirsen 30 mg/kg
Reporting group description: Subjects who received 30 mg/kg eteplirsen or placebo once weekly, intravenous (IV) infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 30 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.	
Reporting group title	Eteplirsen 50 mg/kg
Reporting group description: Subjects who received 50 mg/kg eteplirsen or placebo once weekly, IV infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 50 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.	
Subject analysis set title	Placebo to Eteplirsen
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects who received eteplirsen matched placebo once weekly, IV infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), followed by 30 or 50 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.	
Subject analysis set title	Eteplirsen-Treated Subjects
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received eteplirsen treatment in the parent study 4658-us-201 (NCT01396239) and in this extension study.	

### Primary: Change From Baseline in the 6 Minute Walk Test (6MWT) at Week 240

End point title	Change From Baseline in the 6 Minute Walk Test (6MWT) at Week 240 <sup>[1]</sup>
End point description: This study used a modified version of the 6MWT test procedure described in American Thoracic Society (ATS) 2002 guidelines, specifically adapted for patients with DMD. The subject was asked to walk a set course of 25 meters for 6 minutes (timed) and the distance walked in meters was recorded. Increases from baseline in 6MWT distance are indicative of improvement and decreases from baseline indicate worsening. Baseline here corresponds to the baseline in the parent study (4658-us-201, NCT01396239). The Intent-to-Treat Population (ITT) population included all subjects randomized into parent study 4658-us-201. Here, "Number of Subjects analysed" signifies subjects evaluable for this endpoint. Results are reported below in 2 reporting groups based on evaluation period (Week 240) as applicable for this endpoint.	
End point type	Primary
End point timeframe: Parent Baseline and Week 240	

#### 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: Summaries were descriptive and no formal statistical tests were done.

End point values	Eteplirsen 30 mg/kg	Eteplirsen 50 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: Meters				
arithmetic mean (standard deviation)	-199.0 ( $\pm$ 113.25)	-258.0 ( $\pm$ 175.65)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in the Percentage of Dystrophin Positive Fibers (PDPF) at Week 48

End point title	Change From Baseline in the Percentage of Dystrophin Positive Fibers (PDPF) at Week 48 <sup>[2]</sup>
-----------------	---

End point description:

Dystrophin expression as assessed by percent dystrophin positive fibers was measured by immunohistochemistry (IHC) technique using primary anti-dystrophin antibody. Percent change from baseline is the arithmetic difference of the treatment time point minus baseline divided by baseline calculated for individual subjects. Baseline here corresponds to the baseline in the parent study (4658-us-201, NCT01396239). The ITT population included all subjects randomized into parent study 4658-us-201. Results are reported below in 3 reporting groups of placebo to eteplirsen, eteplirsen 30 mg/kg, eteplirsen 50 mg/kg, respectively, based on evaluation period (Week 48) as applicable for this endpoint.

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

End point timeframe:

Parent Baseline and Week 48

Notes:

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

Justification: Summaries were descriptive and no formal statistical tests were done.

End point values	Eteplirsen 30 mg/kg	Eteplirsen 50 mg/kg	Placebo to Eteplirsen	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	4	4	
Units: Percentage Fibers				
arithmetic mean (standard deviation)	51.69 (± 7.089)	42.93 (± 13.433)	37.70 (± 12.602)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Parent Baseline up to 240 weeks (cumulative Study 4658-us-201 + 4658-us-202)

Adverse event reporting additional description:

Only treatment-emergent adverse events with an onset data on or after the date of first dose of study drug were reported. Relatedness of serious adverse events to study medication was determined by the Investigator.

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

### Dictionary used

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

Dictionary version	14.0
--------------------	------

### Reporting groups

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

Reporting group description:

Subjects who received 30 mg/kg eteplirsen or placebo once weekly, IV infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 30 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.

Reporting group title	Eteplirsen 50 mg/kg
-----------------------	---------------------

Reporting group description:

Subjects who received 50 mg/kg eteplirsen or placebo once weekly, IV infusion for 24 weeks in the parent study 4658-us-201 (NCT01396239), continued the same treatment with 50 mg/kg eteplirsen once weekly for 212 weeks (up to Week 240) in this extension study.

Serious adverse events	Eteplirsen 30 mg/kg	Eteplirsen 50 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Tibia fracture	Additional description: Not related to study medication. All events are related to patients falling.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture	Additional description: Not related to study medication. All events are related to patients falling.		
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders Acute respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Not related to study medication.		
	1 / 6 (16.67%)	0 / 6 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders Scoliosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Not related to study medication.		
	2 / 6 (33.33%)	0 / 6 (0.00%)	
	0 / 2	0 / 0	
	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Eteplirsen 30 mg/kg	Eteplirsen 50 mg/kg	
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Vascular disorders Haematoma subjects affected / exposed occurrences (all)  Flushing subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1  0 / 6 (0.00%) 0	1 / 6 (16.67%) 1  1 / 6 (16.67%) 1	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)  Catheter site pain subjects affected / exposed occurrences (all)  Infusion site extravasation	1 / 6 (16.67%) 3  2 / 6 (33.33%) 2	2 / 6 (33.33%) 2  2 / 6 (33.33%) 3	

subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	2
Device occlusion		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1
Infusion site haematoma		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1
Oedema peripheral		
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	7	0
Thrombosis in device		
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	3	1
Application site erythema		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Application site pruritus		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Catheter site haematoma		
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	3
Catheter site haemorrhage		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Catheter site inflammation		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Catheter site related reaction		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Chest pain		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Influenza like illness		

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infusion site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infusion site rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infusion site urticaria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Reproductive system and breast disorders			
Pelvic pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Testicular pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 5	4 / 6 (66.67%) 15	
Nasal congestion subjects affected / exposed occurrences (all)	5 / 6 (83.33%) 11	2 / 6 (33.33%) 3	
Cough subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	4 / 6 (66.67%) 12	
Epistaxis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 6 (33.33%) 4	
Pharyngeal erythema subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 6 (50.00%) 6	
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	0 / 6 (0.00%) 0	
Upper respiratory tract congestion subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	
Productive cough			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sneezing			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	4 / 6 (66.67%)	
occurrences (all)	0	4	
C-reactive protein increased			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Blood glucose increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Blood creatine phosphokinase increased			

subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	
Body height below normal subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	
Activated partial thromboplastin time abnormal subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Blood urea increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2	
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 3	
Red blood cells urine positive subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2	
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Wound healing normal subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	5 / 6 (83.33%) 8	6 / 6 (100.00%) 11	
Contusion			

subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)
occurrences (all)	9	12
Arthropod bite		
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	4	2
Excoriation		
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	2	11
Joint injury		
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	1
Joint sprain		
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	3
Muscle strain		
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	2
Fall		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Foot fracture		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1
Incision site haemorrhage		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1
Incision site pain		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Arthropod sting		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Back injury		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Burns first degree		

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Cardiac function disturbance postoperative		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Compression fracture		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Concussion		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Head injury		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Laceration		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1
Limb injury		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1
Lip injury		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Lower limb fracture		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Nail injury		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Post procedural haematoma		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Postoperative respiratory distress		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0

Radius fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Humerus fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Scratch			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Torus fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Ulna fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
<b>Congenital, familial and genetic disorders</b>			
Cryptorchism			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
<b>Cardiac disorders</b>			
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
<b>Nervous system disorders</b>			
Headache			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	
occurrences (all)	31	12	

Balance disorder subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	3 / 6 (50.00%) 3	
Dizziness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Sinus headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Somnolence subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	
Ear and labyrinth disorders Cerumen impaction subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Motion sickness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Tympanic membrane disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Eye disorders Cataract subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 6 (33.33%) 2	
Cataract subcapsular			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Erythema of eyelid			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Hypermetropia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	
occurrences (all)	8	6	
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	
occurrences (all)	2	7	
Dyspepsia			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	
occurrences (all)	3	3	
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	1	7	
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	
occurrences (all)	2	7	
Oral pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	1	3	

Abdominal discomfort		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	7	1
Dental caries		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Dysphagia		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Flatulence		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Food poisoning		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Haemorrhoids		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Lip swelling		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Retained deciduous tooth		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Tooth impacted		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Toothache		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Gastritis		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Tooth disorder		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0

Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Rash			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Ecchymosis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	1	3	
Papule			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Dermatitis bullous			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Intertrigo			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Keloid scar			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nail discolouration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nail dystrophy			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Rash papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin erosion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	3	
Urticaria thermal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	
occurrences (all)	2	5	
Glycosuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Hypercalciuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Growth hormone deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cushingoid			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	
occurrences (all)	11	15	
Arthralgia			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	
occurrences (all)	8	9	
Back pain			
subjects affected / exposed	6 / 6 (100.00%)	3 / 6 (50.00%)	
occurrences (all)	13	8	
Muscle spasms			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	2	3	
Musculoskeletal pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	4	3	
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	4	
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Scoliosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tendon disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Foot deformity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	
occurrences (all)	6	10	
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	
occurrences (all)	9	13	
Gastroenteritis viral			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	2	3	
Hordeolum			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	7	
Post procedural cellulitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	

Viral infection		
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	2
Candidiasis		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Incision site infection		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	2
Pharyngitis streptococcal		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Sinusitis		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Tinea capitis		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Tinea pedis		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Viral upper respiratory tract infection		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	3
Folliculitis		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1

Abscess			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Abscess limb			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Bacterial disease carrier			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Paraspinal abscess			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Dehydration			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Obesity			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Vitamin D deficiency			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2012	<p>Amendment 1</p> <ul style="list-style-type: none"><li>• Text suggesting that dosing adjustments might be made via protocol amendment was removed from the protocol as the Sponsor did not intend to change the dosing regimen.</li><li>• A brief high-level summary of safety data from the recently completed parent study, Study 4658-us-201, was added.</li><li>• The protocol was corrected to indicate that blood for biomarker assessments should be drawn at the satellite sites once the patient has been transferred to their satellite site.</li><li>• The protocol was corrected to specify that brief physical examinations should be performed every week when the patient receives study medication. In addition, full physical examinations are performed at the central site at the times specified in the Schedule of Events.</li><li>• Guidelines for the timing of drug administration, and for taking planned drug holidays to accommodate scheduling conflicts, were added to the protocol to improve the clarity of the document and provide increased convenience for the patients, respectively.</li><li>• The Week 44 assessments (Week 72 for combined 201/202 studies) fell during the winter holidays, and were therefore moved to Week 46 (Week 74 for combined 201/202 studies) because it was anticipated that travel to the central site would be difficult during this time.</li></ul>
04 October 2012	<p>Amendment 2</p> <ul style="list-style-type: none"><li>• Instructions for eteplirsen administration were clarified for consistency with the study's Pharmacy Manual.</li><li>• The option of inserting an implanted venous access port for eteplirsen administration was added.</li></ul>
26 February 2013	<p>Amendment 3</p> <ul style="list-style-type: none"><li>• Removed the collection of blood samples for ELISPOT analyses at Weeks 56, 68, and 80 (Weeks 84, 96, and 108 for combined 201/202 studies) because no immune response has been observed in samples collected to date and all boys have been expressing dystrophin since Week 48 (Week 76 for combined 201/202 studies).</li><li>• The statistical analyses were updated.</li></ul>
16 May 2013	<p>Amendment 4</p> <ul style="list-style-type: none"><li>• The study was extended from 80 weeks to 164 weeks of treatment.</li></ul>
03 February 2014	<p>Amendment 5</p> <ul style="list-style-type: none"><li>• PK sample collection was added to Week 124 assessments (Week 152 for combined 201/202 studies).</li><li>• The option of receiving at-home infusions of study drug by a visiting nurse after Week 124 (Week 152 for combined 201/202 studies) was added.</li></ul>
21 May 2014	<p>Amendment 6</p> <ul style="list-style-type: none"><li>• A second, optional biopsy was added at Week 132 (Week 160 for combined 201/202 studies) for patients who consent to this procedure. The purpose of this optional biopsy is gain additional data on eteplirsen-induced dystrophin expression after more than 2 years of eteplirsen treatment.</li></ul>

14 August 2014	<p>Amendment 7</p> <ul style="list-style-type: none"> <li>• Extended the study an additional 48 weeks (End of Study = Week 212 [Week 240 for combined 201/202 studies])</li> <li>• Rescheduled timing for optional muscle biopsy from Week 132 (Protocol Version 06) to between Week 140 and Week 152 (to between Week 168 and Week 180 for combined 201/202 studies)</li> <li>• Updated name of investigational product to "eteplirsen injection" from AVI-4658 Concentrate for Injection"</li> <li>• Changed infusion time from a minimum of 60 minutes to 35 to 60 minutes</li> <li>• Allowed decrease of the postinfusion observation period from 60 minutes to 30 minutes</li> <li>• Added end date (Week 46 [Week 74 for combined 201/202 studies]) for ELISPOT collection</li> <li>• Removed urine cystatin C from laboratory assessments</li> <li>• Updated Schedule of Events table so that ECHO, ECG, and height could be collected on either Day 1 or Day 2 at functional assessment visits after Week 92 (Week 120 for combined 201/202 studies)</li> </ul>
08 December 2015	<p>Amendment 8</p> <ul style="list-style-type: none"> <li>• Duration of study was extended from a total of 212 weeks to a total of 236 weeks of treatment to permit continued administration of eteplirsen until it becomes commercially available.</li> <li>• Defined the primary treatment period as the period from baseline through Week 212 (Week 240 for combined 201/202 studies), after which efficacy assessments were discontinued.</li> <li>• Added collection of blood and urine samples at Week 212 (Week 240 for combined 201/202 studies) for the determination of eteplirsen concentrations and PK.</li> <li>• Added a SFU visit to occur 4 weeks after the last eteplirsen infusion if patients do not continue eteplirsen after study completion or discontinuation.</li> </ul>
01 July 2016	<p>Amendment 9</p> <ul style="list-style-type: none"> <li>• The study duration was extended from 236 weeks (264 weeks for combined 201/202 studies) to 284 weeks (312 weeks for combined 201/202 studies), plus a 4-week SFU visit. The period following the Week 212 (combined Week 240) was defined as the Safety Extension period, during which patients continue to receive weekly eteplirsen infusions and undergo safety assessments.</li> <li>• Added a full physical examination to the SFU visit.</li> </ul>

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>