



## Clinical trial results:

### An Open-Label, Multi-Center Study to Evaluate the Safety and Tolerability of Eteplirsen in Patients With Advanced Stage Duchenne Muscular Dystrophy

#### Summary

EudraCT number	2016-005024-28
Trial protocol	Outside EU/EEA
Global end of trial date	23 March 2018

#### Results information

Result version number	v1
This version publication date	28 March 2019
First version publication date	28 March 2019

#### Trial information

##### Trial identification

Sponsor protocol code	4658-204
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02286947
WHO universal trial number (UTN)	-
Other trial identifiers	4658-204: Study Number

Notes:

#### Sponsors

Sponsor organisation name	Sarepta Therapeutics, Inc.
Sponsor organisation address	215 First Street, Cambridge, United States, 02142
Public contact	Medical Director, Sarepta Therapeutics, Inc., +1 6172744000, clinicaltrials@sarepta.com
Scientific contact	Medical Director, Sarepta Therapeutics, Inc., +1 6172744000, clinicaltrials@sarepta.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001722-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 October 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 March 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To explore safety and tolerability of eteplirsen in patients with advanced stage Duchenne muscular dystrophy (DMD) who are amenable to exon 51 skipping.

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	04 November 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: 24
Worldwide total number of subjects	24
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)	9
Adolescents (12-17 years)	12
Adults (18-64 years)	3
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was conducted at 9 sites in the United States from November 2014 to March 2018.

### Period 1

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

### Arms

<b>Arm title</b>	Eteplirsen 30 mg/kg
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Arm description:

Subjects received eteplirsen 30 milligram per kilogram (mg/kg) intravenous (IV) infusion, once weekly, for 96 weeks.

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

Dosage and administration details:

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

<b>Number of subjects in period 1</b>	Eteplirsen 30 mg/kg
Started	24
Completed	22
Not completed	2
Consent withdrawn by subject	2

## Baseline characteristics

### Reporting groups

Reporting group title	Eteplirsen 30 mg/kg
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Reporting group description:

Subjects received eteplirsen 30 milligram per kilogram (mg/kg) intravenous (IV) infusion, once weekly, for 96 weeks.

Reporting group values	Eteplirsen 30 mg/kg	Total	
Number of subjects	24	24	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	12	12	
Adults (18-64 years)	3	3	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	12.9		
standard deviation	± 3.30	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	24	24	

## End points

### End points reporting groups

Reporting group title	Eteplirsen 30 mg/kg
Reporting group description:	
Subjects received eteplirsen 30 milligram per kilogram (mg/kg) intravenous (IV) infusion, once weekly, for 96 weeks.	

### Primary: Number of Subjects With Treatment Emergent Adverse Events

End point title	Number of Subjects With Treatment Emergent Adverse
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#### End point description:

An AE was any untoward medical occurrence in a subject that did not necessarily have a causal relationship with the study drug. An SAE was an AE resulting in any of the following outcomes: death; Life-threatening event; Required or prolonged inpatient hospitalization; persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs were events that developed or worsened during the on-treatment period (defined as time from first dose of study drug and up to 28 days after last dose of study drug [up to 100 weeks] that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious adverse events. Analysis was performed on safety population which included all subjects who received at least 1 dose of eteplirsen.

End point type	Primary
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#### End point timeframe:

From first dose of drug up to 100 weeks

#### 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 analyzed for this endpoint.

<b>End point values</b>	Eteplirsen 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects	24			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities
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#### End point description:

Laboratory parameters included hematology, clinical chemistry, urinalysis and coagulation. Data is only reported for parameters in which at least 1 subject had potentially clinically significant abnormal findings. Analysis was performed on safety population which included all subjects who received at least 1 dose of eteplirsen.

Incr=increase; LLN=lower limit of normal; ULN=upper limit of normal; GGT=gamma glutamyl transferase

End point type	Secondary
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End point timeframe:

Baseline up to 100 weeks

End point values	Eteplirsen 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects				
Sodium: Decrease of 8 or more	3			
Sodium: Increase of 8 or more	3			
Potassium: Decrease of 1.1 or more	2			
Potassium: Increase of 1.0 or more	2			
Potassium: Value > 5.5 or < 3.0	1			
Calcium: Decrease of 0.30 or more	1			
Glucose: Decrease of 3.1 or more	1			
Glucose: Increase of 3.2 or more	6			
Albumin: Value < LLN or > ULN	4			
Bilirubin: Incr of 10 or more	1			
Bilirubin: Value > 1.5 x ULN	1			
Alanine Aminotransferase: Value >= 2 x Baseline	1			
GGT: value > 3*Baseline or > ULN	2			
Lactate Dehydrogenase: Value >= 2 x Baseline	1			
Creatine Kinase: Value >= 2 x Baseline	5			
Hemoglobin: Value < LLN	5			
Hematocrit: Value < LLN	7			
Red Blood Cell: Value < LLN	4			
White Blood Cell: Value < LLN or > 1.5 x ULN	5			
Platelets: Value < 150 or < 200	1			
Neutrophils: Value > 1.5 x ULN or < 1000	7			
Lymphocytes: Value < LLN	6			
Monocytes: Value < LLN	14			
Eosinophils: Value > 1.5 x ULN or < LLN	2			
Basophils: Value < LLN or > ULN	2			
Urine Protein: Value > 1+	5			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs
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End point description:

Vital sign parameters included systolic blood pressure (SBP), diastolic blood pressure (DBP) in millimeters of mercury (mmHg), heart rate (HR), and body temperature. Data is only reported for parameters in which at least 1 subject had potentially clinically significant abnormal vital sign findings. Analysis was performed on safety population which included all subjects who received at least 1 dose of eteplirsen.

End point type	Secondary
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End point timeframe:

Baseline up to 100 weeks

End point values	Eteplirsen 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects				
DBP: Less than 40 mmHg	1			
DBP: Greater than 90 mmHg	12			
SBP: Less than 80 mmHg	4			
SBP: Greater than 130 mmHg	17			
HR: Less than 50 beats per minute (bpm)	1			
HR: Greater than 130 bpm	15			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With at Least One Abnormal Physical Examination Finding

End point title	Number of Subjects With at Least One Abnormal Physical Examination Finding
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End point description:

Physical examinations, full and brief, were performed by the Investigator, a physician Sub-Investigator, or a Nurse Practitioner (if licensed in the state or province to perform physical examinations). Full physical examinations included examination of general appearance; head, ears, eyes, nose, and throat; heart; lungs; chest; abdomen; skin; lymph nodes; and musculoskeletal and neurological systems. Brief physical examinations included examination of general appearance; head, ears, eyes, nose, and throat; heart; lungs; chest; abdomen; and skin. Analysis was performed on safety population which included all subjects who received at least 1 dose of eteplirsen.

End point type	Secondary
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End point timeframe:

Baseline up to 100 weeks

<b>End point values</b>	Eteplirsén 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects	23			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Abnormalities in Electrocardiograms (ECGs)

End point title	Number of Subjects With Abnormalities in Electrocardiograms (ECGs)
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End point description:

Twelve-lead ECGs and Holter ECGs were performed at a consistent time of day throughout the study. ECGs were performed only after the subject was in the supine position, resting, and quiet for a minimum of 15 minutes. The ECG was manually reviewed and interpreted by medically qualified personnel using a central vendor according to prespecified criteria. The Investigator reviewed the results of the centrally read ECG report and determined if the findings were clinically significant. Data is only reported for parameters in which at least 1 subject had potentially clinically significant abnormal ECG findings. Analysis was performed on safety population which included all subjects who received at least 1 dose of eteplirsén.

msec=milliseconds; QTcF=QT interval corrected with Fridericia's method

End point type	Secondary
End point timeframe:	
Baseline up to 100 weeks	

<b>End point values</b>	Eteplirsén 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects				
Heart Rate: >120 beats/minute	6			
QTcF: Increase of 60 or more msec	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Abnormalities in Echocardiograms (ECHO)

End point title	Number of Subjects With Abnormalities in Echocardiograms (ECHO)
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End point description:

Standard, 2-dimensional ECHOs were performed at a consistent time of day throughout the study. The ECHO was reviewed and interpreted by medically qualified personnel using a central vendor according to prespecified criteria. Ejection fraction was noted. The Investigator reviewed the results of the ECHO report and determined if the findings were clinically significant. Analysis was performed on safety population included which all subjects who received at least 1 dose of eteplirsén.

LEVF=left ventricular ejection fraction

End point type	Secondary
End point timeframe:	
Baseline up to 100 weeks	

<b>End point values</b>	Eteplirsen 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects				
LEVF: < 55%	0			
Fractional Shortening: < 28%	6			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 100

Adverse event reporting additional description:

Safety population included all subjects who received at least 1 dose of eteplirsen.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Eteplirsen 30 mg/kg
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Reporting group description:

Subjects received eteplirsen 30 mg/kg, IV infusions, once weekly, for 96 weeks.

Serious adverse events	Eteplirsen 30 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extremity contracture			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Eteplirsen 30 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Investigations			
Breath sounds abnormal			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Protein urine present			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	16		
Joint injury			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Foot fracture			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Skin abrasion			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Soft tissue injury			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 24 (8.33%)</p> <p>2</p>			
<p>Spinal compression fracture</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 24 (8.33%)</p> <p>2</p>			
<p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 24 (8.33%)</p> <p>2</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>8 / 24 (33.33%)</p> <p>18</p>			
<p>General disorders and administration site conditions</p> <p>Catheter site bruise</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 24 (12.50%)</p> <p>4</p> <p>Catheter site pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>5 / 24 (20.83%)</p> <p>7</p> <p>Chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 24 (8.33%)</p> <p>3</p> <p>Infusion site bruising</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>4 / 24 (16.67%)</p> <p>5</p> <p>Infusion site pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 24 (8.33%)</p> <p>3</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 24 (12.50%)</p> <p>4</p>			
<p>Gastrointestinal disorders</p> <p>Abdominal discomfort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 24 (12.50%)</p> <p>3</p> <p>Abdominal pain upper</p>			

subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	7		
Cough			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	13		
Oropharyngeal pain			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	7		
Rhinorrhoea			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Throat irritation			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Acne			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Rash papular			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	8 / 24 (33.33%)		
occurrences (all)	9		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	13		
Muscle spasms			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Osteoporosis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Infections and infestations			

Ear infection subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 24 (58.33%) 23		
Gastroenteritis subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 4		
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 7		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2014	The overall reason for the amendment was to add a safety extension period to allow continued treatment with eteplirsen for an additional 48 weeks.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported