

**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 | <ul style="list-style-type: none">• 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) | 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? | 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 (\pm 72.36) | -2.3 (\pm 14.95) | -17.3 (\pm 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 occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 2 / 4 (50.00%) 2 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 1 / 4 (25.00%) 1 | 2 / 4 (50.00%) 5 |
| Nasal congestion subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 2 / 4 (50.00%) 2 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 4 (75.00%) 4 | 0 / 4 (0.00%) 0 | 3 / 4 (75.00%) 4 |
| Sinus congestion subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Upper respiratory tract congestion subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Back injury | | | |

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

| | | | |
|---|---|---|---|
| subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Ear and labyrinth disorders Motion sickness subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 1 / 4 (25.00%) 2 1 / 4 (25.00%) 1 2 / 4 (50.00%) 3 | 2 / 4 (50.00%) 2 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 0 / 4 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) Petechiae subjects affected / exposed occurrences (all) Urticaria thermal subjects affected / exposed occurrences (all) | 2 / 4 (50.00%) 2 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 |
| Renal and urinary disorders Polyuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 1 / 4 (25.00%) 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 | <p>Version 2 (Amendment 1)</p> <ul style="list-style-type: none">* 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 | <p>Version 3 (Amendment 2)</p> <ul style="list-style-type: none">* 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 | <p>Version 4.0 (Amendment 3)</p> <ul style="list-style-type: none">* 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. |

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| 10 August 2011 | <p>Version 5.0 (Amendment 4)</p> <ul style="list-style-type: none"> * Clarified that the 6MWT would be administered twice during the Screening visit and that the mean of the 2 assessments \pm 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 \geq 110 bpm and symptomatic. * Added collection of serum cystatin C to the list of safety laboratory assessments. |
| 08 September 2011 | <p>Version 6.0 (Amendment 5)</p> <ul style="list-style-type: none"> * 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 eteplirsén. |
| 04 November 2011 | <p>Version 7.0 (Amendment 6)</p> <ul style="list-style-type: none"> * 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 | <p>Version 8.0 (Amendment 7)</p> <ul style="list-style-type: none"> * 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 eteplirsén to which they were placebo-matched while those who received 50 or 30 mg/kg/wk eteplirsén for the first 24 weeks would continue to receive the same dose regimen of eteplirsén without interruption. * Specified that treatment assignment during the first 24 weeks of the study (eteplirsén 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>