# 1 TITLE PAGE

## 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

**PROTOCOL NUMBER:** 4658-US-201

**TEST DRUG:** eteplirsen

**INDICATION:** Duchenne Muscular Dystrophy

**STUDY PHASE:** 2

**STUDY DATES:** 18 July 2011 to 29 February 2012

**SPONSOR:**
Sarepta Therapeutics Inc.
215 First St.
Cambridge, MA 02142
Phone: 617-274-4000

**DATE:** Final 01 October 2014

This study was conducted in compliance with Good Clinical Practices, including the archiving of essential documents.

[redacted]

# 2 SYNOPSIS

| **Name of Sponsor/Company** | **Name of Finished Product** | **Name of Active Ingredient** |
|---|---|---|
| Sarepta Therapeutics Inc.<br>*(formerly AVIBioPharma)* | | eteplirsen |

**Protocol Number:** 4658-us-201

**Title of Study**: 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

**Investigators and Study Centers:** Jerry R. Mendell MD; Nationwide Children's Hospital, Columbus, Ohio, USA

**Publication (reference):** Not applicable at this time.

| | | |
|---|---|---|
| **Study Period (months):** | 7.5 | **Phase of Development:** 2 |
| **Date of First Enrollment:** | 18 July 2011 | |
| **Date of Last Completed:** | 29 February 2012 | |

**Objectives:** This study was designed to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of eteplirsen (AVI-4658) at 50 and 30 mg/kg/week (wk) doses in patients diagnosed with Duchenne muscular dystrophy (DMD).

**Methodology:** This was a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of once-weekly intravenous (IV) infusions of eteplirsen in patients with genotypically confirmed DMD with an appropriate genetic lesion. While the safety and efficacy assessments were performed at a single institution, patients were recruited nationally.

Eligible patients were randomized to receive 50 or 30 mg/kg/wk eteplirsen or placebo; after 24 weeks, placebo patients were further randomized to 1 of 2 groups to create 4 treatment groups as shown below. Groups 1 and 2 received 50 or 30 mg/kg/wk eteplirsen for 28 weeks, while Group 3a received placebo once a week for 24 weeks followed by 50 mg/kg/wk eteplirsen for 4 weeks, and Group 3b received placebo once a week for 24 weeks followed by 30 mg/kg/wk eteplirsen for 4 weeks.

| Group | Treatment/Dose of Eteplirsen | N |
|---|---|---|
| 1 | 50 mg/kg/wk eteplirsen for 28 weeks | 4 |
| 2 | 30 mg/kg/wk eteplirsen for 28 weeks | 4 |
| 3a | Placebo for 24 weeks followed by 50 mg/kg/wk eteplirsen for 4 weeks | 2 |
| 3b | Placebo for 24 weeks followed by 30 mg/kg/wk eteplirsen for 4 weeks | 2 |

The patients, Investigator, study staff, Sponsor and contract research organization personnel (except a statistician and individual(s) authorized to dispense study medication) were blinded as to whether a patient received eteplirsen or placebo for the first 24 weeks of this study through study completion. Beginning Week 25, all parties were aware that all patients were receiving either 50 or 30 mg/kg/wk eteplirsen during the last 4 weeks of the study.

All patients received a pre-treatment biopsy of the biceps muscle within 4 weeks prior to the first administration of study drug. Patients in Groups 1 and 3a underwent a repeat biopsy in the contralateral biceps

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muscle at Week 12, while those in Groups 2 and 3b underwent a repeat biopsy at Week 24. Efficacy and PK were measured at scheduled visits while safety and tolerability were continuously monitored.

All patients who completed this study were eligible to continue eteplirsen in an open-label extension study (Study 4658-us-202).

**Number of Patients (planned and analyzed):** Twelve patients were planned and enrolled to participate in this study which was conducted at a single investigative site.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria**

A patient had to meet all of the following criteria to be eligible for this study.

1. Be a male with DMD and have an out-of-frame deletion(s) that may be corrected by skipping exon 51 (e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63), as confirmed in a Clinical Laboratory Improvement Act (CLIA)-accredited laboratory by any of the peer-reviewed and published methodology that evaluates all exons (including, but not limited to, multiplex ligation-dependent probe, comparative genomic hybridization, and single-condition amplification/internal primer analysis).
2. Be between the ages of 7 and 13 years, inclusive.
3. Have stable cardiac function and stable pulmonary function (forced vital capacity [FVC] ≥50% of predicted and not require supplemental oxygen) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Be receiving treatment with oral corticosteroids and have been on a stable dose for at least 24 weeks before study entry. Patients may be allowed to take other (except for RNA antisense or gene therapy) medication,including angiotensin-converting enzyme [ACE] inhibitors, β-blockers, losartan potassium, and coenzyme Q, as long as they have been on a stable dose of the medication for 24 weeks before the screening visit (visit 1) and the dose will remain constant throughout the study.
5. Have intact right and left biceps muscles or an alternative upper arm muscle group.
6. Achieve an average distance within 200 m and 400 m ±10% (i.e. within 180 m and 440 m) while walking independently over 6 minutes.
7. Have a left ventricular ejection fraction (LVEF) of >40% based on the echocardiogram (ECHO) that is obtained at the screening visit (visit 1). A patient who has abnormal ECHO findings but who has an LVEF of >40% may be enrolled in the study at the Investigator's discretion; however, the patient must have been receiving stable doses of ACE inhibitors or β-blockers for at least 24 weeks before study entry.
8. Have a parent(s) or legal guardian(s) who is able to understand and comply with the all of the study procedure requirements.
9. Be willing to provide informed assent and have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

**Exclusion Criteria**

A patient who met any of the following criteria was to be excluded from this study.

1. Use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength or function within 12 weeks before study entry (e.g., growth hormone, anabolic steroids).
2. Previous treatment with the experimental agents eteplirsen, BMN-195, or PRO051.

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3. Previous treatment with any other experimental agents or participation in any other DMD interventional clinical study within 12 weeks before entry into this study; including use of the shock training system or "STS," or planned use during this study.
4. Surgery within 3 months before study entry or planned surgery at any time during this study.
5. Presence of other clinically significant illness at the time of study entry, including significant renal dysfunction (as measured by urinary cystatin C, kidney injury molecule (KIM)-1, or urinary total protein), or average heart rate during screening Holter monitoring in excess of 110 bpm (unless subsequently treated and confirmed controlled and stable on a β-blocker) or QTc >450 ms.
6. Use of any aminoglycoside antibiotic within 12 weeks before the screening visit (visit 1) or need for use of an aminoglycoside antibiotic during the study (unless discussed and agreed with the Principal Investigator and Medical Monitor).
7. Prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient or that makes it unlikely that the course of treatment or follow-up would be completed or could impair the assessment of study results.

**Test Product, Dose and Mode of Administration, Batch Number:** Test product was 30 or 50 mg/kg/wk eteplirsen administered once a week. Eteplirsen was supplied as a sterile, isotonic, clear, colorless phosphate buffered saline (PBS) solution at a concentration of 100 mg/mL in single-use vials without preservatives. Eteplirsen was diluted into a 150 mL bag of normal saline and administered by intravenous (IV) infision over a period of 60 minutes. It was recommended that a topical anesthetic cream (lidocaine 2.5%, prilocaine 2.5%) be applied to the infusion site prior to each administration of study drug. All patients were observed for at least 4 hours after their first infusion and for at least 1 hour following all subsequent infusions. Batch numbers of eteplirsen used in this study were: 60GD-DE01 and 68GD-DE01.

**Duration of Treatment:** 28 weeks

**Reference Therapy, Dose and Mode of Administration, Batch Number:** The reference treatment, PBS, was administered in an identical fashion to eteplirsen and was visually indistinguishable from the test peoduct. The batch number of PBS used in this study was 65EF-DD01.

**Endpoints for Evaluation:**

**Efficacy:** The primary efficacy endpoint was the change from baseline in the percentage of dystrophin-positive fibers as measured in muscle biopsy tissue using immunohistochemistry (IHC) at Week 12 for the 50 mg/kg/wk eteplirsen and matching placebo groups (Groups 1 and 3a) and at Week 24 for the 30 mg/kg/wk eteplirsen and matching placebo groups (Groups 2 and 3b).

Additional biopsy-related endpoints included change from baseline to Week 12 for Groups 1 and 3a and to Week 24 for Groups 2 and 3b in:

- dystrophin intensity levels as measured by IHC
- total dystrophin protein levels as measured by Western blot analysis
- exon skipping as measured by reverse transcription polymerase chain reaction (RT-PCR)
- CD3, CD4, and CD8 lymphocyte counts as measured by IHC

Functional efficacy endpoints included change from baseline to week 24 in the:

- 6-Minute Walk Test (6MWT)
- Timed 4-Step Test
- Maximum Voluntary Isometric Contraction Test (MVICT)
- North Star Ambulatory Assessment (NSAA) total score, and NSAA components including the Timed 10-Meter Run and rise time

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- 9-Hole Peg Test
- Pulmonary Function Testing (PFT) including forced vital capacity (FVC), percent predicted FVC (%FVC), forced expiratory volume in 1 second ($FEV_1$), percent predicted $FEV_1$ ($\%FEV_1$), $FEV_1$/FVC ratio; maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP)

Change from baseline to week 24 on the Pediatric Quality of Life Inventory (PedsQL) was an additional endpoint.

**Safety:** The safety and tolerability of eteplirsen through Week 28 were assessed through an evaluation of:

- The frequency and severity of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs
- Safety laboratory tests including hematology, coagulation, and serum chemistry assays (including serum cystatin C) and urinalysis (including urinary cystatin C and KIM-1)
- Immune response to dystrophin as assessed by enzyme-linked immunosorbent spot assay (ELISPOT).
- Vital signs
- Physical examinations
- 12-lead electrocardiograms (ECGs)
- ECHO

**Pharmacokinetics:** The PK of eteplirsen was determined from multiple plasma and urine samples collected over 24 hours post-end of infusion on Week 12 and at 5 post-end of infusion on Weeks 24 and 25. PK parameters for eteplirsen were calculated using non-compartmental analysis. Actual sampling times were used in all final PK analyses. Per protocol times were used to calculate mean plasma concentrations for graphical displays.

The PK parameters characterized included time ($T_{max}$) and value of maximum plasma concentration ($C_{max}$), the apparent volume of distribution at steady state ($V_{ss}$), the elimination half-life ($t_{½}$), areas under the plasma concentration-curve (AUC), total clearance (CL), mean residence time (MRT), and renal (i.e., urinary) clearance ($Cl_R$).

**Statistical Methods:**

All available data were included in data listings. No imputation of values for missing data was performed. Placebo-treated patients were pooled for the purpose of statistical summaries and inferential statistical analyses.

Summary statistics consisted of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD) or, as appropriate, the standard error of the mean (SE), minimum, and maximum values for continuous variables.

Baseline for all quantitative safety measures (laboratory parameters, vital signs, and 12-lead ECG measurements) was defined as the last valid evaluation done before the study drug administration on week 1.

A blinded interim safety analysis was performed by an independent Data Safety Monitoring Board (DSMB) after the patients in Groups 1 and 3a completed the Week 12 muscle biopsy, and again after Groups 2 and 3b completed the Week 24 muscle biopsy.

Primary Endpoint: The primary efficacy endpoint was the change from baseline in the percentage of dystrophin-positive fibers as measured in muscle tissue using IHC at Week 12 for patients who received 50 mg/kg/wk eteplirsen and at Week 24 for patients who received 30 mg/kg/wk eteplirsen vs. placebo. The primary efficacy endpoint was analyzed by comparing the 50 mg/kg/wk eteplirsen treatment group (Group 1) at Week 12 to the combined placebo treatment group (Groups 3a and 3b), and the 30 mg/kg/wk eteplirsen treatment group (Group 2) at Week 24 to the combined placebo treatment group using the change from baseline values. An analysis of covariance (ANCOVA) for ranked data was used for these analyses with

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baseline values and duration of DMD as covariates.

**Summary of Results:**

**Patient Disposition:** All 12 patients received all scheduled infusions of study medication and completed the study as planned. No safety concerns were identified by the DSMB at any point during the study and the study was completed without interruption.

**Key Demographics:** All patients were male and, except for one patient of Asian descent, all were white. At baseline, patients had a mean age of 8.8 years, a mean height of 123.7 centimeters (cm), a mean weight of 31.5 kg, and a mean body mass index (BMI) of 20.4 kg/$m^2$. Compared to the other groups, patients in the 30 mg/kg/wk group were slightly older, heavier, and taller at baseline, and they achieved a shorter distance on the 6MWT.

**Efficacy Results:**

- Once weekly treatment with 30 mg/kg eteplirsen for 24 weeks significantly increased the mean percentage of dystrophin-positive muscle fibers in DMD-treated patients compared to placebo ($p \leq 0.002$) to meet the study's pre-specified primary efficacy endpoint.
- Patients treated with 30 mg/kg/wk eteplirsen demonstrated an increase from baseline in the mean percentage of dystrophin-positive fibers to 41.1% of normal at Week 24. In contrast, there were no detectable increases from baseline in the mean percentage of dystrophin-positive fibers in placebo-treated patients biopsied at Weeks 12 or 24. There were also no detectable mean increases from baseline in patients treated with the higher dose of 50 mg/kg/wk and biopsied at Week 12.
- Treatment with 50 mg/kg/wk eteplirsen for 12 weeks or 30 mg/kg/wk for 24 weeks increased mean dystrophin fiber intensity levels to 19.5% and 21.2% of normal, respectively. In contrast, the mean post-treatment dystrophin intensity level in placebo-treated patients was 9.2%% of normal.
- Consistent with its effects on the percentage of dystrophin-positive fibers, treatment with 30 mg/kg/wk eteplirsen for 24 weeks appeared to increase the mean total amount of dystrophin protein more than placebo or 50 mg/kg/wk eteplirsen for 12 weeks as measured in muscle tissue homogenates by Western blot.
- Performance on measures involving ambulation including the 6MWT, Timed 4-Step Test, and several components of the NSAA was highly variable with some patients showing minor improvements from baseline, most remaining stable, and 2 patients in the 30 mg/kg/wk eteplirsen group showing marked decline within weeks of the first dose. When those 2 patients were excluded from the analyses of these measures (modified intent-to-treat [mITT] analyses), there were no meaningful differences between the groups.
- Changes in other functional efficacy endpoints including the MVICT, 9-Hole Peg Test, and PFT were generally small with no clear differentiation observed between the eteplirsen and placebo groups.

**Pharmacokinetic Results:**

- Plasma concentrations at 5 minutes post end of infusion were similar between 12 and 24 weeks on active drug for each dose level.
- Between the 30 and 50 mg/kg/wk dose levels, $C_{max}$ increased in a manner proportional with dose, whereas AUC increased in a somewhat greater than proportional manner.
- $CL_{PL}$, $V_{ss}$ and half-life were similar at both dose levels.
- Given eteplirsen's half-life of about 3 hours and the rapid decline in plasma concentrations over 24

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hours, little if any accumulation would be expected upon repeated once-weekly dosing of eteplirsen.

- Renal clearance of intact eteplirsen accounted for approximately two-thirds of total systemic clearance.

The PK profile of eteplirsen given as a 1-hour IV infusion was similar to that previously reported in the DMD patient population in study AVI-4658-28.

**Safety Results:**

- IV infusions of 30 or 50 mg/kg/wk eteplirsen for 28 weeks were well tolerated.
- A total of 99 treatment emergent adverse events (TEAEs) were reported, most of which were related to the required muscle biopsies or were consistent with signs and symptoms typically seen in pediatric patients and those with DMD. The most commonly reported TEAEs included procedural pain, oropharyngeal pain, [redacted], cough, nasal congestion, and extremity pain. No relationship between the occurrence of specific TEAEs and treatment (placebo vs. eteplirsen) or dose of eteplirsen (50 vs. 30 mg/kg/wk) was observed.
- All TEAEs but 1 (nausea in a placebo-treated patient) were assessed as unrelated to study medication, and all but 3 (nasal congestion, bone pain and transient loss of balance in two 30 mg/kg/wk eteplirsen-treated patients) were assessed as mild or moderate in intensity.
- There were no SAEs, discontinuations due to AEs, or deaths.
- Change from baseline in safety laboratory tests (chemistry, coagulation, hematology, and urinalysis), measures of renal function (serum cystatin C, urine cystatin C and KIM-1), and vital signs were generally small and no trends related to treatment (placebo vs. eteplirsen) or dose level of eteplirsen (30 vs. 50 mg/kg/wk) were observed. In addition, no abnormal safety laboratory findings (including measures of renal function) or changes from baseline in vital signs were assessed as clinically significant. One placebo-treated patient experienced transient and mild proteinuria during Week 8 that was considered an AE.
- Changes from baseline in cardiac function tests (ECG and ECHO) were generally small and none were assessed as clinically significant.
- There were no clear differences between the placebo- and eteplirsen-treated patients in the number of interferon-γ induced spot forming colonies to dystrophin peptide indicating that the newly expressed dystrophin in the eteplirsen-treated patients did not elicit a T-cell response.

**Conclusions:**

Intravenous infusions of eteplirsen at doses of 30 or 50 mg/kg/wk for up to 28 weeks were well-tolerated in this sample of boys with DMD. Exon 51 skipping was demonstrated post-treatment in 100% of patients, and duration-of-treatment-dependent, rather than dose-dependent increases in dystrophin expression were observed in the mean percentage of dystrophin-positive fibers and dystrophin fiber intensity levels. When balanced against the progressive and ultimately fatal nature of DMD, the current findings demonstrate that treatment with eteplirsen for 24 weeks induces production of dystrophin, the protein necessary for muscle function, in patients with DMD who are amenable to exon 51 skipping treatment. These promising results support the continued evaluation of eteplirsen to confirm that the observed induction of dystrophin protein production in treated patients will translate into measurable clinical benefit.

**01 October 2014**

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# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation/Term | Definition |
|---|---|
| 2D | 2-dimensional |
| 3D | 3-dimensional |
| $\%AUC_{\infty,ex}$ | percentage of $AUC_{\infty}$ obtained by extrapolation |
| 6MWT | 6-Minute Walk Test |
| ACE | angiotensin-converting enzyme |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under plasma concentration-time curve |
| $AUC_{0-\infty}$ | area under the concentration-time curve extrapolated to infinity |
| $AUC_{0-24}$ | area under the plasma concentration-time curve from time 0 to 24 hours post infusion |
| $AUC_{0-last}$ | area under the concentration-time curve from 0 to last measurable concentration |
| ATS | American Thoracic Society |
| BLQ | below the limit of quantification |
| BMD | Becker muscular dystrophy |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CK | creatine kinase |
| CLIA | Clinical Laboratory Improvement Act |
| $CL_R$ | renal clearance |
| $C_{max}$ | maximum observed concentration |
| CMH | Cochran's-Mantel Haenszel statistic |
| $C_{trough}$ | trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose |
| CRF | case report form |
| CRP | C-reactive protein |
| DMD | Duchenne muscular dystrophy |
| DSMB | Data Safety Monitoring Board |
| ECG | electrocardiogram |

| | |
|---|---|
| ECHO | echocardiogram |
| eCRF | electronic case report form |
| EDB | extensor digitorum brevis |
| EF | ejection fraction |
| ELISPOT | enzyme-linked immunosorbent spot |
| FDA | US Food and Drug Administration |
| $FEV_1$ | forced expiratory volume in 1 second |
| $\%FEV_1$ | forced expiratory volume in 1 second percent predicted |
| FS | fractional shortening |
| FVC | forced vital capacity |
| %FVC | forced vital capacity percent predicted |
| GCP | Good Clinical Practices |
| GGT | gamma-glutamyl transferase |
| hDMD | human Duchenne muscular dystrophy mouse model |
| HEENT | head, ears, eyes, nose, throat |
| HR | heart rate |
| ICH | International Conference on Harmonization |
| IHC | Immunohistochemistry, including immunofluorescence methodology |
| IM | intramuscular, intramuscularly |
| INR | international normalized ratio |
| IRB | institutional review board |
| IV | intravenous, intravenously |
| KIM-1 | kidney injury molecule -1 |
| LDH | lactate dehydrogenase |
| LOCF | last observation carried forward |
| LVEF | left ventricular ejection fraction |
| MedDRA® | Medical Dictionary for Regulatory Activities® |
| MEP | maximum expiratory pressure |
| MIP | maximum inspiratory pressure |
| mITT | modified intent-to-treat |
| MMRM | mixed model repeated measures |
| MRT | mean residence time |
| MVICT | Maximum Voluntary Isometric Contraction Test |
| NCH | Nationwide Children's Hospital |
| NMM | Neuromuscular Module (of PedsQL) |

| | |
|---|---|
| NSAA | North Star Ambulatory Assessment |
| PBS | phosphate buffered saline |
| PC | predefined change |
| PCA | predefined change abnormal |
| PedsQL™ | Pediatric Quality of Life Inventory™ |
| PFTs | pulmonary function tests |
| PK | pharmacokinetic |
| PMO | phosphorodiamidate morpholino oligomer |
| PR | the interval from the beginning of the P wave to the beginning of the QRS complex; representing atrioventricular conduction time |
| PT | prothrombin time; preferred term |
| QMA | Quantitative Movement Assessment |
| QRS | the interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization |
| QT | the interval from the beginning of the QRS complex to the end of the T wave, representing the total duration of electrical activity of the ventricles |
| QTc | corrected QT interval |
| RBC | red blood cells |
| REML | restricted maximum likelihood |
| RT-PCR | reverse transcription polymerase chain reaction |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SE | standard error |
| SF | shortening fraction |
| SOC | system organ class |
| SOP | standard operating procedures |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| $t_{max}$ | time to maximum plasma concentration |
| US/USA | United States |
| $Vd_{ss}$ | apparent volume of distribution at steady-state |
| WBC | white blood cell |
| WHO | World Health Organization |
| wk | week |

# 5 ETHICS

## 5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocol and informed consent/assent forms used in this study were reviewed and approved by the institutional review board (IRB) of the study site before any patient was enrolled in the study. The study Investigator was responsible for obtaining IRB approval of all protocol amendments before implementation, for reporting any serious or unexpected adverse events (AEs), for reporting any other information that may have affected the safe use of the study drug, and for submitting yearly progress reports and a final report at the completion of the study to the IRB.

Copies of the protocol and its 7 amendments are provided in [redacted], information regarding the electronic case report forms (eCRFs) is provided in [redacted] and a list of all IRBs consulted is provided in [redacted]

## 5.2 Ethical Conduct of the Study

The study was conducted in full compliance with the Principles of the Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, and the US Code of Federal Regulations (CFR), 21 CFR Part 50 & 312. The study was registered on ClinicalTrials.gov under identification number NCT01396239.

## 5.3 Patient Information and Consent

In obtaining and documenting informed consent and assent, the Investigator complied with all applicable regulatory requirement(s), and adhered to Good Clinical Practice (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki.

Before undertaking any study-related procedures with patients, the purpose and nature of the study as well as possible adverse effects were explained to them and their parents or legal guardians in understandable terms. Written informed consents were obtained from the parents or legal guardians of all patients and informed assent was obtained from all patients ≥9 years of age. Patients and their parents or legal guardians were given copies of the signed informed consent/assent forms.

Samples of the forms used are provided in [redacted]

# 6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted at a single site, Nationwide Children's Hospital (NCH) in Columbus, Ohio, under the Principal Investigator, Dr. Jerry Mendell. A list of key study personnel is provided below in Table 6-1. A list of study personnel, a description of their role in the study, and their qualifications, is provided in [redacted]. The Data Safety Monitoring Board (DSMB), charter, including the list of members, is also provided in [redacted]. Signed approval of the Clinical Study Report from the Principal Investigator and from the Sponsor's responsible medical officer are provided in [redacted]

**Table 6-1: Study Administrative Structure**

| | |
|---|---|
| Study Site | Nationwide Children's Hospital<br>700 Children's Drive<br>Columbus, Ohio 43205<br>614-722-2000 |
| Principal Investigator | Jerry R. Mendell, MD<br>Curran-Peters Chair in Pediatric Research<br>Professor of Pediatrics and Neurology<br>Director Gene Therapy Center and<br>Director of Paul D. Wellstone Center<br>Nationwide Children's Hospital and The Ohio State University |
| Sponsor | Sarepta Therapeutics Inc. *(formerly AVIBioPharma)*<br>215 First St.<br>Cambridge, MA 02142 USA<br>617-274-4000 |
| Chief Medical Officer | Edward M. Kaye, MD<br>Senior Vice President and Chief Medical Officer<br>Sarepta Therapeutics Inc. |
| Medical Monitor | [redacted]<br>Pia Mikkelsen Lynch, MD<br>Lynch Consulting Group, Inc. |
| Statistician | Jay B. Saoud, PhD<br>Senior Director, Biometrics<br>Sarepta Therapeutics Inc. |
| Clinical Operations | [redacted]<br>Senior Director of Clinical Operations<br>Sarepta Therapeutics Inc. |
| Lead Report Author | [redacted]<br>Manager, Medical Writing<br>Sarepta Therapeutics Inc. |
| Contract Research Organizations | [redacted] |

**Table 6-1: Study Administrative Structure**

| | |
|---|---|
| Contract Research Organizations | [redacted] |
| Central Laboratories | Nationwide Children's Hospital Laboratory<br>Myriad (RBM)– KIM-1 and cystatin-C analysis |
| Pharmacokinetic Analysis | [redacted]<br>McMinnville, OR 97128 USA<br><br>Pharmacokinetic (PK) Report Author: [redacted] |
| Functional Efficacy Assessments (e.g., 6MWT, NSAA, PFT) | Physical Therapists at Nationwide Children's Hospital:<br>Linda Lowes, PT, PhD<br>Lindsay Alfano, PT, DPT, PCS<br>[redacted] |
| Dystrophin Analyses and Verification of Exon Skipping | Nationwide Children's Hospital Laboratory |
| Electrocardiogram and Echocardiography | [redacted]<br>Nationwide Children's Hospital |
| Clinical Study Supply Management | [redacted] |

# 7 INTRODUCTION

The purpose of this study was to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of once weekly intravenous (IV) infusions of eteplirsen (AVI-4658) compared to placebo in patients with Duchenne muscular dystrophy (DMD) who were amenable to exon 51 skipping.

**Duchenne Muscular Dystrophy**

DMD is a degenerative disease with an X-linked recessive inheritance caused by mutations in the dystrophin gene. The mutations that cause DMD disrupt the mRNA reading frame and prohibit production of dystrophin, a critically important part of the protein complex that connects the cytoskeleton of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of muscle contraction causes progressive muscle damage. The clinical effect of this disrupted dystrophin reading frame is dramatic and lethal.

DMD is usually first diagnosed between the ages of 3 to 5 years (Ciafaloni 2009), when toddlers develop a waddling gait, lordosis, toe walking, calf hypertrophy, and difficulty climbing stairs. Over time, ambulation becomes increasingly abnormal. By 8 years of age, most patients are losing the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking leading to the increased use of mobility devices such as strollers and scooters. Patients with DMD spend less time walking than healthy boys and walk more slowly than healthy boys (McDonald 2005), and are significantly less active than healthy boys of similar age (McDonald 2002, McDonald 2005). By 10 to 14 years of age, most are wheelchair dependent. Weakness of the arms and increasingly limited upper limb function, contractures, decubitus ulcers, and scoliosis (which often requires surgery) occur frequently. While pulmonary and cardiac function are generally normal during early childhood, cardiac and diaphragmatic muscles progressively weaken during adolescence and patients often require ventilation support. Historically, patients typically died from respiratory or cardiac failure in their late teens or early 20s (Brooke 1989, Eagle 2002). Recent research suggests that use of ventilation support and steroids may increase life span by several years; however, DMD still has a mortality rate of 100% (Kohler 2009). Currently, only palliative treatments exist for DMD. These include corticosteroids, which can prolong ambulation and reduce the incidence of severe scoliosis; however, they are often associated with serious sequelae (Biggar 2006; Manzur 2004) and are not always employed.

**Eteplirsen**

Sarepta Therapeutics Inc. (Sarepta) is developing eteplirsen for the treatment of DMD. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO), which is a novel class of synthetic antisense oligonucleotide molecules based on a fundamental redesign of the natural nucleic acid structure. PMOs bind to complementary sequences of RNA by standard nucleic acid base-pairing, but are different from RNA and DNA in that their nucleic acid bases are bound to 6-member, synthetic morpholine rings instead of ribose (as in RNA) or deoxyribose (as in DNA) rings, and are linked through charge-neutral phosphorodiamidate moieties instead of negatively charged phosphodiesters.

Eteplirsen is designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. In doing so, eteplirsen restores the reading frame for patients with deletions in exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63 of this gene, and enables the production of an internally truncated, yet functional dystrophin protein, similar to that observed in Becker muscular dystrophy (BMD). BMD is an allelic form of muscular dystrophy characterized by mutations that result in the production of an internally truncated, but still active dystrophin protein (Bushby 1993a, Heald 1994, Muntoni 2003). Accordingly, unless affected by severe cardiomyopathy, most BMD patients remain ambulatory and have a near-normal life expectancy (Bushby 1993b).

Ongoing treatment with eteplirsen is expected to result in sustained production of functional dystrophin protein and improve the quality of life and prognosis for DMD patients, essentially switching their clinical symptoms and prognosis to be more similar to those of patients with BMD. This hypothesis is supported by results of nonclinical studies in primary muscle cells of DMD patients and in the human DMD (*hDMD*) mouse model showing that eteplirsen induces skipping of exon 51 and results in the production of internally truncated, functional dystrophin protein (Arechavala-Gomeza 2007). More direct support for the potential efficacy of eteplirsen derives from results of the eteplirsen clinical studies completed to date.

**Prior Clinical Experience with Eteplirsen**

Two phase 1, open-label clinical studies of eteplirsen provide initial support for the safety and potential efficacy of eteplirsen in the treatment of DMD. In the first study, AVI-4658-33, seven nonambulatory DMD boys aged 10 to 16 years received a single intramuscular (IM) dose of eteplirsen 0.09 mg (n = 2) or 0.9 mg (n = 5) in the extensor digitorum brevis (EDB) muscle of one foot and a single IM dose of placebo in the opposite foot. The 5 patients who received the 0.9 mg dose showed evidence of exon skipping (detected by RT-PCR), an increase in the percentage of dystrophin-positive fibers (detected by IHC), and increased dystrophin protein (detected by Western blot) in the eteplirsen-treated foot, but not the placebo-treated foot. In the second study, AVI-4658-28, 19 DMD boys aged 6 to 13 years received up to 12 weekly IV infusions of eteplirsen at doses of 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/week (wk). Two weeks after the last dose of eteplirsen, exon 51 skipping was detected in 100% of 17 evaluable patients, and increases in the percentage of dystrophin-positive fibers and dystrophin intensity were detected in 65% (11/17) of the evaluable patients. Patients in the 2 highest dose groups (10 and 20 mg/kg/wk) had the largest and most consistent increases in dystrophin production. Eteplirsen was well tolerated in both studies; most AEs were assessed as mild to moderate in intensity and were related to the biopsy procedures and/or the underlying disease as opposed to eteplirsen itself. Moreover, laboratory assessments, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and pulmonary function tests (PFTs) were generally stable over the course of both studies. Additional information on the safety of eteplirsen is available in the Investigator's Brochure.

**Study 4658-us-201**

In light of these positive findings, Study 4658-us-201 was initiated in July 2011. The study was designed to assess the efficacy, safety, tolerability, and PK of weekly IV infusions of eteplirsen. Efficacy was primarily based on the effect of eteplirsen on dystrophin expression in target

muscle. In addition, because walking difficulty is one of the earliest and most serious complications of DMD, the effect of eteplirsen on ambulation relative to placebo was assessed with a widely used and validated measure of walking ability and endurance, the 6-Minute Walk Test (6MWT) (McDonald 2010a). To increase the likelihood that study patients would be at a similar stage of disease progression at study entry and that they would be able to complete all of the intended efficacy assessments, eligibility was restricted to patients who had been on a stable dose of corticosteroids for at least 6 months prior to screening and who were able to achieve an average effective distance between 180 m and 440 m on the 6MWT. Study conduct was overseen by an independent DSMB and interim analyses of safety data by the DSMB were performed. The study design was submitted to the Food and Drug Administration (FDA) Division of Neurology Products on 24 September 2010, and the Division provided written recommendations on 21 January 2011. The protocol was further discussed during a Type B end-of-phase-1 meeting between Sarepta and the Division on 14 June 2011.

# 8 STUDY OBJECTIVES

This study was designed to assess the efficacy, safety, tolerability, and PK of eteplirsen at 50 mg/kg/wk and 30 mg/kg/wk doses in patients diagnosed with DMD.

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan: Description

This was a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of once-weekly IV infusions of eteplirsen in patients with genotypically confirmed DMD with an appropriate genetic lesion.

Eligible patients were randomized to receive 50 or 30 mg/kg/wk eteplirsen or placebo for 24 weeks; placebo patients were then further randomized to 1 of 2 groups to create 4 treatment groups as shown below in Table 9-1. Groups 1 and 2 received 50 or 30 mg/kg/wk eteplirsen for 28 weeks, while Group 3a received placebo once a week for 24 weeks followed by 50 mg/kg/wk eteplirsen for 4 weeks, and Group 3b received placebo once a week for 24 weeks followed by 30 mg/kg/wk eteplirsen for 4 weeks.

The patients, Investigator, study staff, Sponsor, and contract research organization personnel (except an unblinded statistician who produced the actual randomization schedule and individuals authorized to verify dose and assignment and/or dispense study medication) were blinded to treatment assignment for the first 24 weeks of this study. Unblinded individuals could not interact with the patients, and were instructed not to divulge the randomization assignment to others under any circumstances, unless directed to do so by the Investigator in the interests of the patient's safety after the occurrence of a serious adverse event (SAE). Beginning Week 25, all parties were aware that all patients were receiving eteplirsen during the last 4 weeks of the study, but they remained blinded as to which treatment they had received previously in the study.

**Table 9-1: Treatment Groups**

| Group | Treatment/Dose of Eteplirsen | N |
|---|---|---|
| **1** | 50 mg/kg/wk eteplirsen for 28 weeks | **4** |
| **2** | 30 mg/kg/wk eteplirsen for 28 weeks | **4** |
| **3a** | Placebo for 24 weeks then 50 mg/kg/wk eteplirsen for 4 weeks | **2** |
| **3b** | Placebo for 24 weeks then 30 mg/kg/wk eteplirsen for 4 weeks | **2** |

All patients received a pre-treatment biopsy of the biceps muscle within 4 weeks prior to the first administration of study drug. Patients in Groups 1 and 3a underwent a repeat biopsy in the contralateral biceps muscle at Week 12, while those in Groups 2 and 3b underwent a repeat biopsy in the contralateral biceps at Week 24. Analysis of biopsy samples by IHC was performed according to written procedures in a central laboratory by blinded personnel who were not otherwise involved in the study. Efficacy and PK were measured at scheduled visits while safety and tolerability were continuously monitored. The safety of the study participants was monitored by the DSMB.

All patients who completed this study were eligible to continue eteplirsen treatment in an open-label extension study, Study 4658-us-202.

## 9.2 Discussion of Study Design, Including the Choice of Control Groups

This study was designed to assess the efficacy, safety, tolerability, and PK of eteplirsen in patients with DMD. Randomized patients were administered IV infusions of placebo, 30 mg/kg/wk or 50 mg/kg/wk eteplirsen for 24 weeks. The 24-week treatment period for this study was selected to ensure sufficient time for production of de novo dystrophin and increase the chances that clinical benefit might be observed. Under Amendment 7 (Section 9.7.9.1), the treatment period was extended by 4 additional weeks so that patients could transition to a planned open-label extension study (4658-us-202) without an interruption in dosing. Patients in Groups 1 and 2 who were already receiving 50 or 30 mg/kg/wk eteplirsen continued their dosing regimen for an additional 4 weeks, while those in Groups 3a and 3b received 50 or 30 mg/kg/wk eteplirsen, respectively, for the last 4 weeks.

All patients had a pre-treatment biopsy of the biceps muscle within 4 weeks prior to the first administration of study drug. Follow-up biopsies were taken from the opposite biceps at staggered time points, depending on dose group, to evaluate the impact of treatment duration on novel dystrophin production.

Randomization was used to avoid bias in the assignment of patients to eteplirsen or placebo, to increase the likelihood that known and unknown patient attributes (e.g., demographic and baseline characteristics) were evenly balanced across the treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment (eteplirsen vs. placebo) was used to reduce potential bias during data collection and evaluation of data.

The choice of a placebo control group for this study was largely dictated by the fact that no disease modifying treatments for DMD are currently available. Of note, all patients, regardless of treatment assignment, were required to be on a stable dose of corticosteroids at study entry and to remain on that dose (as clinically indicated) for the duration of the study. This requirement was implemented to ensure that all patients received the current standard of care while participating in this study and to minimize between-patient variability in disease progression that would likely arise if only a subset of patients were using corticosteroids or if dosing regimens were altered significantly during the course of the trial.

The rationale for selection of doses for this study is presented in Section 9.4.4. The appropriateness of the efficacy and safety assessments used in this study is discussed in Section 9.5.5.

## 9.3 Selection of Study Population

### *9.3.1 Inclusion Criteria*

Patients had to meet all of the following criteria to be eligible for this study:

1. Be a male with DMD and have an out-of-frame deletion(s) that may be corrected by skipping exon 51 [e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63], as confirmed in a Clinical Laboratory Improvement Act (CLIA)-accredited laboratory by any peer-reviewed and published methodology that evaluates all exons (including, but not limited to, multiplex ligation-dependent probe, comparative genomic hybridization, and single condition amplification/internal primer analysis).

2. Be between the ages of 7 and 13 years, inclusive.

3. Have stable cardiac function and stable pulmonary function (forced vital capacity [FVC] ≥50% of predicted and not require supplemental oxygen) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.

4. Be receiving treatment with oral corticosteroids and have been on a stable dose for at least 24 weeks before study entry. Patients may be allowed to take other (except RNA antisense or gene therapy) medication, including angiotensin-converting enzyme [ACE] inhibitors, β-blockers, losartan potassium, and coenzyme Q, as long as they have been on a stable dose of the medication for 24 weeks before the screening visit (Visit 1) and the dose will remain constant throughout the study.

5. Have intact right and left biceps muscles or an alternative upper arm muscle group.

6. Achieve an average distance within 200 and 400 meters ±10% (i.e. within 180 and 440 meters) while walking independently over 6 minutes.

7. Have a left ventricular ejection fraction (LVEF) of >40% based on the ECHO that is obtained at the screening visit (Visit 1). A patient who has abnormal ECHO findings but who has an LVEF of >40% may be enrolled in the study at the Investigator's discretion; however, the patient must have been receiving stable doses of ACE inhibitors or β-blockers for at least 24 weeks before study entry.

8. Have a parent(s) or legal guardian(s) who is able to understand and comply with the all of the study procedure requirements.

9. Be willing to provide informed assent and have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

### *9.3.2 Exclusion Criteria*

Patients who met any of the following criteria were excluded from this study:

1. Use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength or function within 12 weeks before study entry (e.g., growth hormone, anabolic steroids).

2. Previous treatment with the experimental agents eteplirsen, BMN-195, or PRO051.

3. Previous treatment with any other experimental agents or participation in any other DMD interventional clinical study within 12 weeks before entry into this study; including use of the shock training system or "STS," or planned use during this study.

4. Surgery within 3 months before study entry or planned surgery at any time during this study.

5. Presence of other clinically significant illness at the time of study entry, including significant renal dysfunction (as measured by urinary cystatin C, KIM-1, or urinary total protein), or average heart rate during screening Holter monitoring in excess of 110 bpm

(unless subsequently treated and confirmed controlled and stable on a β-blocker) or QTc >450 ms.

6. Use of any aminoglycoside antibiotic within 12 weeks before the screening visit (Visit 1) or need for use of an aminoglycoside antibiotic during the study (unless discussed and agreed with the Principal Investigator and Medical Monitor).
7. Prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient or that makes it unlikely that the course of treatment or follow-up would be completed or could impair the assessment of study results.

### *9.3.3 Removal of Patients from Therapy or Assessment*

Patients were free to withdraw consent and/or discontinue study treatment and/or discontinue participation in this study at any time without prejudice. A patient's study treatment or their participation in the study could also be discontinued at any time at the discretion of the Investigator or Sponsor. If a patient withdrew formal consent, the Investigator was to make a reasonable effort to determine the cause. The Investigator was also to make a reasonable effort to ensure that any patient who discontinued study medication for any reason completed all required study procedures if possible.

A patient's treatment or participation in this clinical study could have been prematurely discontinued as a result of:

- The patient withdrew assent or the patient's parent or legal guardian withdrew consent to participate in the study.
- The Investigator determined that it was in the patient's best interest to be withdrawn from the study.
- The patient developed a concomitant illness or other safety concerns arose.
- The patient was lost to follow up.

No patient prematurely discontinued treatment or participation in this study (Section 10.1).

## 9.4 Treatment(s)

### *9.4.1 Treatment(s) Administered*

Eligible patients received IV infusions of 50 mg/kg/wk eteplirsen, 30 mg/kg/wk eteplirsen, or placebo (phosphate buffered saline; PBS) once a week for up to 28 weeks as shown below.

**Table 9-2: Treatment Groups**

| Group | Treatment/Dose of Eteplirsen | N |
|---|---|---|
| **1** | 50 mg/kg/wk eteplirsen for 28 weeks | 4 |
| **2** | 30 mg/kg/wk eteplirsen for 28 weeks | 4 |
| **3a** | Placebo for 24 weeks then 50 mg/kg/wk eteplirsen for 4 weeks | 2 |
| **3b** | Placebo for 24 weeks then 30 mg/kg/wk eteplirsen for 4 weeks | 2 |

Study drug was diluted into a 150 mL bag of normal saline to prepare a double-blind infusion and was administered by IV infusion over a period of 60 minutes. It was recommended that a topical anesthetic cream (lidocaine 2.5%, prilocaine 2.5%) be applied to the infusion site prior to each infusion.

Placebo was administered in an identical fashion and study drug and placebo infusion solutions were visually indistinguishable.

All patients were observed for at least 4 hours after their first infusion and for at least 1 hour following all subsequent infusions.

### *9.4.2 Identity of Investigational Product(s)*

Eteplirsen was supplied as a sterile, isotonic, clear, colorless PBS solution at a concentration of 100 mg/mL in single-use vials without preservatives.

Placebo was supplied as vials of clear, colorless PBS identical in appearance to eteplirsen.

The lot numbers that were used in the study are summarized by treatment in [redacted] Patients receiving each batch are identified in [redacted]

**Table 9-3: Eteplirsen and Placebo Lot Numbers**

| Treatment | Lot Numbers |
|---|---|
| **Eteplirsen** | 60GD-DE01 |
| | 68GD-DE01 |
| [redacted] | |

### *9.4.3 Method of Assigning Patients to Treatment Groups*

Eligible patients were randomized into double-blind treatment at the first treatment visit on day 1. Randomization was in a 1:1:1 ratio to treatment Groups 1, 2, and 3. Patients randomized

to treatment Group 3 (placebo) were then further randomized in a 1:1 ratio to match the 50 mg/kg/wk dose of eteplirsen (Group 3a-and second muscle biopsy at Week 12) or the 30 mg/kg/wk dose of eteplirsen (Group 3b-and second muscle biopsy at Week 24). Randomization was based upon unstratified permuted block randomization with a block size of 6. A detailed description of the randomization method is provided in [redacted]

### *9.4.4 Selection of Doses in the Study*

The doses of eteplirsen administered in this study, 30 or 50 mg/kg/wk, were expected to be well tolerated based on preclinical data in non-human primates and mice in which maximum feasible doses (320 mg/kg/wk and 960 mg/kg/wk, respectively) were well tolerated when administered for 12 weeks. In addition, in clinical study AVI-4658-28, the highest dose of eteplirsen tested, 20 mg/kg/wk for 12 weeks, was well tolerated by all 4 patients dosed. Moreover, 1 patient in this dose group showed an increase in dystrophin-positive fibers from 3% at baseline to 55% at Week 14. This same patient had approximately 50% greater $C_{max}$ (maximum observed concentration) and AUC (area under the concentration curve) of eteplirsen than the remaining 3 patients in that group, suggesting that higher doses of eteplirsen could lead to a more consistent response in dystrophin expression.

### *9.4.5 Selection and Timing of Dose for Each Patient*

All patients received once weekly IV infusions of eteplirsen or placebo. Infusions were administered over a period of 60 minutes at approximately the same time of day each week. On Weeks 1, 6, 12, and 24, treatment was administered in an in-patient setting with procedures performed over the subsequent 24 hours; all other doses were administered at the study site, but did not necessarily require an overnight stay. The patient's weight was measured prior to each weekly administration and the dose of study drug was calculated based on the patient's weight from the prior visit week.

### *9.4.6 Blinding*

The patients, Sponsor, and all research personnel were blinded to treatment assignment during the first 24 weeks of this study, except for:

- 1 unblinded statistician and 3 statistical programmers who produced data presentations for the DSMB
- 2 unblinded site personnel who verified dose and dispensed study treatment
- 1 unblinded clinical study monitor.

Beginning at Week 25, all parties, including the patients, were aware that all patients were receiving eteplirsen, however, they remained blinded as to the study treatment they had been receiving previously in the study.

The blinding code for Weeks 1 through 24 was not broken during the conduct of this study. Moreover, while the maintenance of the blind was not formally evaluated during this study, none of the study personnel were identified as having been unblinded.

### *9.4.7 Prior and Concomitant Therapy*

The following therapies were not permitted prior to (as specified) or during the conduct of this study:

- Initial prescription of intranasal and/or inhaled and topical steroids for a condition other than DMD in the week before enrollment in this study or during the study period
- Investigational agents for the treatment of DMD within 12 weeks of entry into this study; specifically use of the shock training system or STS or planned use during this study
- Previous exposure to eteplirsen, BMN-195, or PRO051
- Any medication with the potential to affect muscle mass, strength, and/or function, such as, but not limited to, growth hormone, within 12 weeks before enrollment in this study
- Immunosuppressants (other than oral or systemic corticosteroids) during the screening period or while on study
- Use of aminoglycoside antibiotic during the study (unless discussed and agreed with the Principal Investigator and Medical Monitor)

The following therapies could be used prior to and throughout the study; however, attempts to keep the dosage constant throughout the treatment period were to be made:

- Oral corticosteroids including, but not limited to, prednisolone, prednisone, and deflazacort
- Oral ACE inhibitors including, but not limited to, perindopril and lisinopril
- Oral β-blockers (stable dose for 24 weeks) including, but not limited to, carvedilol and atenolol
- Angiotensin-receptor blockers including, but not limited to losartan, irbesartan, valsartan, and candesartan
- Oral laxatives including, but not limited to, lactulose, Senokot, and Movicol
- Vitamin D and calcium supplements
- Over-the-counter herbal preparations, including herbal supplements, vitamins, minerals, and homeopathic preparations, provided the patient had been on stable doses for 24 weeks before enrollment in this study

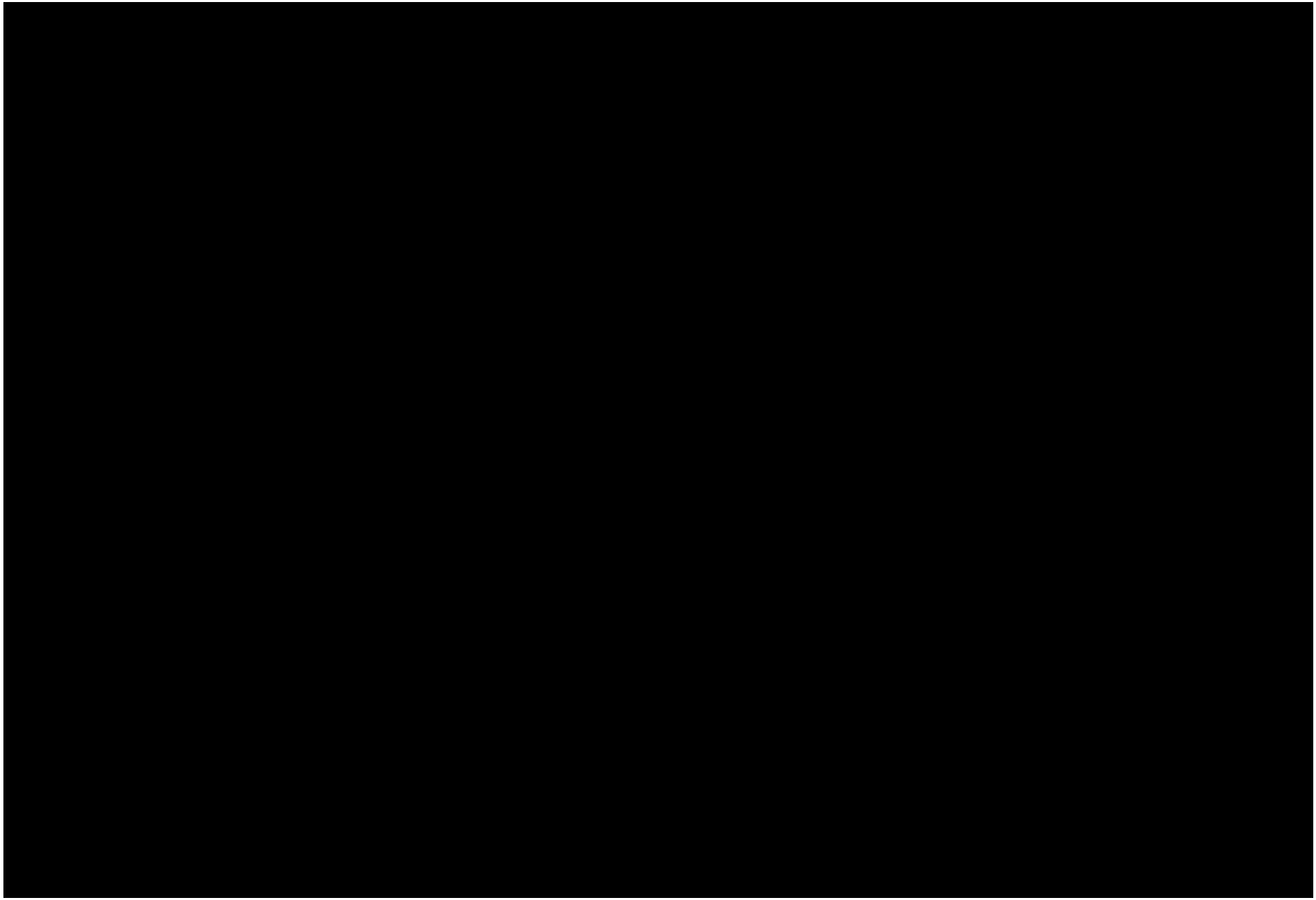
Other concomitant medications (e.g., bisphosphonates or other non-RNA antisense medications) could also be taken, but every attempt was to be made to keep the dosage constant throughout the study period.

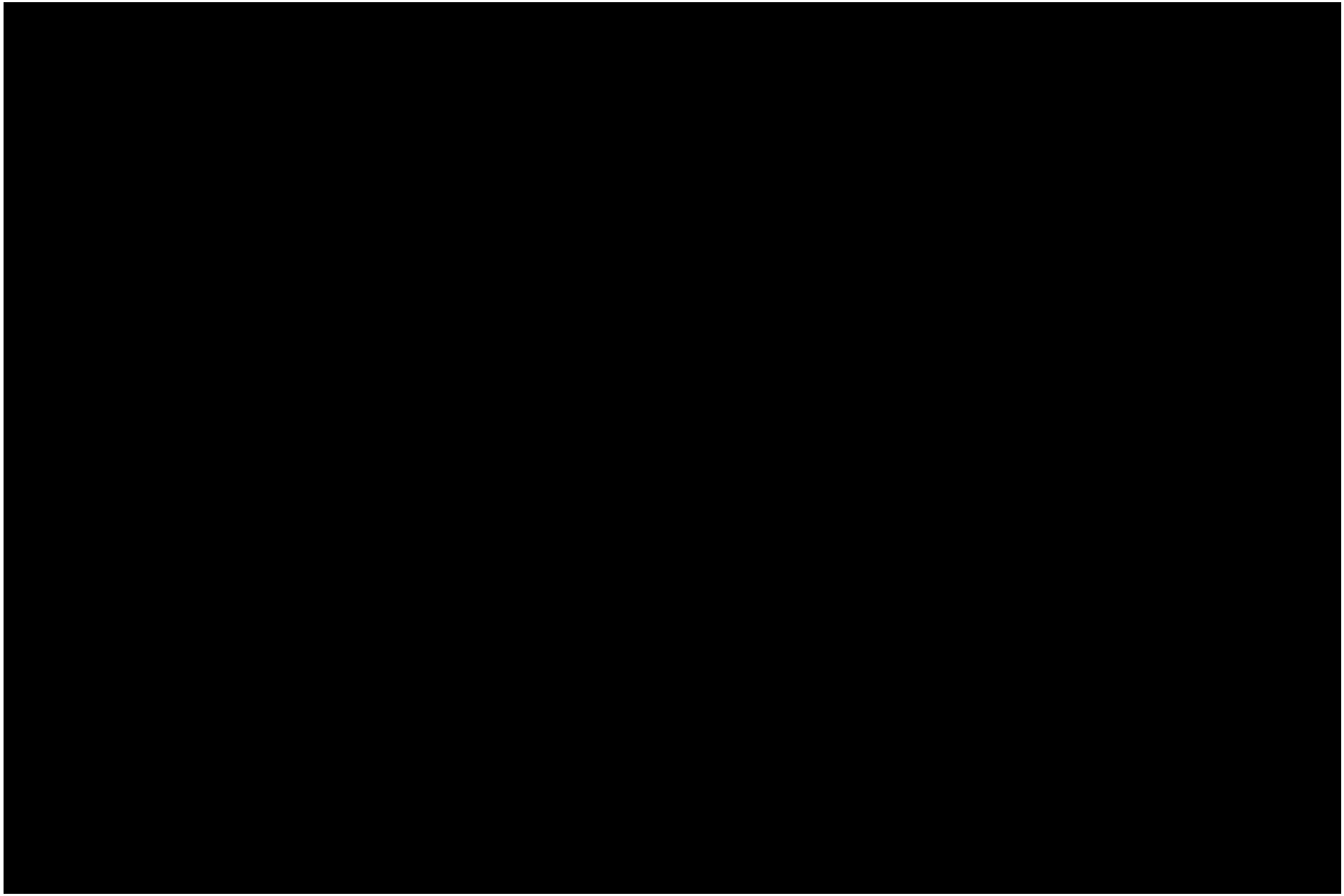
### *9.4.8 Treatment Compliance*

This was a multi-dose study of an IV infusion formulation; each dose was administered to the patient by the Investigator or qualified personnel at the study site. Study drug compliance was assessed using the Study Drug Administration Record that was completed by the investigational site pharmacist.

## 9.5 Efficacy, Safety, and Pharmacokinetic Variables

The schedule of study events, which identifies the assessments performed during this study and their timing, is provided below ([redacted]. The efficacy, safety, and other variables assessed during this study are summarized in subsequent sections.





### *9.5.1 Eligibility, Demographic, Medical History, and Concomitant Medication Assessments*

#### *9.5.1.1 Eligibility*

Genetic analysis for determination of eligibility was completed during screening if results of prior genetic testing were not available. Genetic testing was to be performed by a CLIA-accredited laboratory by any peer-reviewed and published methodology that evaluated all exons.

#### *9.5.1.2 Demography*

Demographic data, including age, sex, ethnicity, and race, were obtained at screening.

#### *9.5.1.3 Medical History*

A standard medical history was obtained at the screening visit by reviewing the patient's medical history and by interviewing the patient/family, and the date of the initial DMD diagnosis was recorded.

#### *9.5.1.4 Concomitant Medications*

Concomitant medications, prescribed or over-the-counter, including herbal supplements, vitamins, minerals, and homeopathic preparations that were taken within 30 days of the first dose of study drug (Week 1) were recorded. Concomitant medications were reviewed at screening and prior to study drug administration throughout the study.

### *9.5.2 Efficacy Assessments*

Efficacy was assessed by evaluation of: dystrophin expression in muscle biopsy tissue using immunohistochemistry (IHC), including immunofluorescence, and Western blot; exon skipping in muscle biopsy tissue using reverse transcription polymerase chain reaction (RT-PCR); lymphocyte infiltration in muscle biopsy tissue using IHC; and muscle strength and function using the 6MWT, the Timed 4-Step Test, the North Star Ambulatory Assessment (NSAA), the Maximum Voluntary Isometric Contraction Test (MVICT), and the 9-Hole Peg Test. Additionally, respiratory function was assessed via standard PFT, and patient quality of life was evaluated using the Pediatric Quality of Life Inventory (PedsQL).

#### *9.5.2.1 Muscle Biopsies*

All muscle biopsies were performed in an inpatient unit at Nationwide Children's Hospital by the same pediatric surgeon using a pre-specified protocol for collection and preparation of tissue. Baseline biopsies were obtained from a biceps muscle [redacted]. Repeat biopsies were obtained from the contralateral biceps muscle at the following time points:

- [redacted] infusion for the 4 patients in the 50 mg/kg/wk treatment group (Group 1) and 2 matching-placebo patients (Group 3a)

- [redacted] infusion for the 4 patients in the 30 mg/kg/wk eteplirsen group (Group 2) and 2 matching placebo patients (Group 3b)

Muscle biopsies were performed under local anesthesia with or without conscious sedation or under general anesthesia, as considered appropriate for a specific patient. During the biopsy procedure, sample tissue of approximately 5 $mm^3$ in size was removed from the patient's biceps muscle. The muscle biopsy sample was then viewed under a stereo dissection microscope to establish fiber orientation. Once fiber orientation was defined, the biopsy sample was mounted according to standard instruction and the mounted biopsy sample was flash-frozen.

#### *9.5.2.2 Evaluation of Dystrophin Expression, Lymphocyte Infiltration, and Exon Skipping in Muscle*

##### 9.5.2.2.1 Percentage of Dystrophin-Positive Fibers

[redacted]

##### 9.5.2.2.2 Dystrophin Intensity Levels

[redacted]

#### 9.5.2.2.3 Dystrophin Protein Levels

[redacted]

#### 9.5.2.2.4 Lymphocyte Infiltration

[redacted]

#### 9.5.2.2.5 Exon Skipping

The exon skipping mechanism of action of eteplirsen was verified by RT-PCR. For each biopsy sample, at least ten 10-µm frozen sections were pooled and homogenized using the RNeasy Plus Universal Mini Kit (Qiagen). Total RNA was subjected to nested RT-PCR using primers specific for dystrophin mRNA, and specific for the mutation in each patient. In all cases, the primers flanked exon 51, such that the mRNA amplicons containing exon 51 were longer than the amplicons of exon 51 skipped mRNA. These 2 amplicons were resolved by electrophoresis on an agarose gel. The RT-PCR products were visualized by ethidium bromide staining and imaging of the gel under ultraviolet light.

### *9.5.2.3 Evaluation of Muscle Strength and Function*

All muscle strength and function assessments were performed by qualified and trained personnel at the study site using the measures described below. Every effort was made to employ the same evaluators for each assessment on each patient throughout the study, and for the assessments to be made at the same approximate time of day.

#### 9.5.2.3.1 6-Minute Walk Test

The 6MWT was performed on Days 1 and 2 of the baseline (Week 1), Week 12, and Week 24 visits and once at the Week 4, 8, 16, and 20 visits as specified in [redacted]. On those visits where 2 tests were performed, the greatest 6MWT distance was used for the principal analysis.

The 6MWT is accurate, reproducible, and easy to administer. It has been used to assess functional capacity, including both strength and endurance, in patients with heart- and lung-related diseases for more than a decade, and is now considered a reliable measure of functional capacity in children with neuromuscular and connective tissue diseases including

Mucopolysaccharidosis I, Mucopolysaccharidosis II, Pompe disease, and DMD (McDonald 2010a; Meunzer 2006; van der Ploeg 2008; Wraith 2004). In the standard test (American Thoracic Society [ATS] 2002), patients are asked to walk a 30-meter course for 6 minutes and the distance walked is recorded. This study used a modified version of the ATS guidelines for the test, which included the addition of a rest period prior to testing, scripted encouragement from the testing staff at regular intervals, and use of a "safety chaser" to walk along behind the participant during testing as described by McDonald (2010a).

Increases from baseline in 6MWT scores are indicative of improvement.

[redacted]

#### 9.5.2.3.3 North Star Ambulatory Assessment

[redacted]

The NSAA is a clinician-administered scale that rates patient performance on various functional activities (Mazzone 2010). During this assessment, patients were asked to perform 17 different functional activities, including a 10 meter walk/run, rising from a sit to stand, standing on 1 leg, climbing stairs, descending stairs, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. Patients were graded as follows: 2 = normal, no obvious modification of activity; 1 = modified method but achieves goal independent of physical assistance from another; and 0 = unable to achieve goal independently.

Increases from baseline in NSAA scores are indicative of improvement.

[redacted]

[redacted]

[redacted]

#### 9.5.2.3.6 *Pulmonary Function Testing*

Pulmonary function testing was performed at the baseline (Week 1), Week 12 and Week 24 visits as specified in Table 9-4 using standard spirometry procedures. The following parameters were recorded: FVC, percent predicted forced vital capacity (%FVC), forced expiratory volume in 1 second ($FEV_1$), percent predicted forced expiratory volume in 1 second (%$FEV_1$), $FEV_1$/FVC ratio, maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP).

Increases from baseline in PFT scores are indicative of improvement.

[redacted]

[redacted]

### *9.5.3 Safety Assessments*

The safety and tolerability of eteplirsen through week 28 were assessed by evaluation of AEs and SAEs, clinical laboratory testing including hematology, coagulation, serum chemistry, and urinalysis, immune response to dystrophin (enzyme linked immunosorbent spot assay; ELISPOT), vital signs, physical examinations, ECGs, and ECHOs.

#### *9.5.3.1 Adverse Events*

Details of AEs/SAEs were recorded from screening through the week 28/early termination visit. On dosing days, the patients were monitored for AEs/SAEs prior to and following study drug administration. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.1 and were reported by primary System Organ Class (SOC) and Preferred Term Name (PT).

***Definition of Adverse Events and Serious Adverse Events***

- Adverse Event (AE): An AE was defined as any untoward medical occurrence in a patient or clinical investigation patient who had been administered a pharmaceutical product, whether or not it was related to the treatment. An AE could therefore include any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not it was considered related to the medicinal product.

- Treatment-Emergent Adverse Event (TEAE): A TEAE was defined as an event that started during or after the first administration of study drug or an event that started before the administration of study drug but that worsened in severity (i.e., became more severe) during or after administration of study drug.

- Serious Adverse Event (SAE): An SAE was defined as any untoward medical occurrence that at any dose:

    - Resulted in death

    - Was life-threatening (i.e., an event in which the patient was at risk of death at the time of the event; not an event that hypothetically might have caused death if it were more severe)

    - Required inpatient hospitalization or prolongation of existing hospitalization

    - Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Resulted in a congenital anomaly/birth defect

In addition, important medical events that were not immediately life-threatening or did not result in death or hospitalization but may have jeopardized the patient or required intervention to prevent one of the other outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, and development of drug dependency or drug abuse) were also considered serious.

***Evaluating and Recording of Adverse Events***

The AE reporting period for this study began at the time the informed consent form was signed and continued through week 28. AEs that occurred before dosing were recorded but were not considered TEAEs unless they worsened in severity after administration of the study drug. Patients who experienced an AE were followed until the AE had resolved, stabilized, or was otherwise explained.

***Assessment of Relationship of Adverse Event to Study Drug***

The Investigator determined the causal relationship between an AE and the study drug based on clinical judgment and the following definitions:

- Unrelated: The event was clearly not related to the investigational agent.
- Possibly/probably related: The event could have been related/was likely related to the investigational agent.
- Definitely related: The event was clearly related to the investigational agent.

AEs that the Investigator considered to be possibly, probably, or definitely related to the study drug were considered as treatment-related AEs.

***Assessment of Intensity of Adverse Events***

The Investigator determined the intensity of the AE using the following definitions:

- Mild: The event did not interfere with the patient's usual activities.
- Moderate: The event interfered with the patient's usual activities.
- Severe: The event prevented the patient from undertaking their usual activities and required therapeutic intervention or cessation of the study drug.

***Assessment of Expectedness of Adverse Events***

The expectedness of any reported serious adverse reaction was to be evaluated using the Investigator's Brochure. Suspected unexpected serious adverse reactions (SUSARs) were to be reported according to regulatory requirements.

### 9.5.3.2 *Clinical Laboratory Tests*

Blood and urine specimens for safety laboratory assessments were obtained at screening and prior to dosing at baseline (Week 1) and Weeks 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 25, and 28 as specified in Table 9-4. The following parameters were evaluated:

- Hematology: Red blood cells (RBC), total white blood cells (WBC), hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells

- Chemistry: Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), total protein, albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), lactate dehydrogenase, C-reactive protein (CRP), Troponin 1, and creatine kinase. Creatinine clearance was calculated by the Cockroft and Gault Formula. Serum cystatin C was evaluated at weeks 1, 12 and 24

- Coagulation: Prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT)

- Urinalysis: pH, specific gravity, protein, glucose, ketones, cytology, hemoglobin, KIM-1 and cystatin C

Immune response to dystrophin (ELISPOT) was evaluated at screening and at Weeks 6, 12, 18, and 24.

### 9.5.3.3 *Physical Examination*

Full physical examinations, which included examination of general appearance, head, ears, eyes, nose and throat (HEENT), heart, lungs, chest, abdomen, skin, lymph nodes, and musculoskeletal and neurological systems, were performed at screening and at Weeks 6, 12, 18, 24, 25, and 28. Brief physical examinations, which included an inspection of the patient's general appearance, heart, lungs, chest, abdomen, and skin were performed at all other weekly visits. Additional physical examinations were done at the Investigator's discretion throughout a patient's participation in the study.

On the first day of dosing, physical examinations were performed within 2 hours before administration of the study drug, post-administration, and at discharge from the clinic. At all other visits examinations were performed pre-administration and at discharge from the clinic.

### 9.5.3.4 *Vital Signs, Weight, and Height*

Vital signs, including temperature, heart rate, respirations and blood pressure were measured at every visit from screening through Week 28.

On dosing days, vital signs were measured [redacted] Vital signs were also measured [redacted] post dosing after the [redacted] infusions.

Weight (recorded in kg) was measured prior to dosing at every visit, while height (recorded in cm) was measured at screening and at Weeks 1 and 24.

#### 9.5.3.4.1 Electrocardiograms

A 12-lead ECG was obtained during screening and [redacted] after administration of study drug at weeks 12 and 24. The ECG was manually reviewed and interpreted by medically qualified personnel and the results and any abnormalities were recorded.

#### 9.5.3.4.2 Echocardiogram

A standard 2-dimensional ECHO was obtained during screening, [redacted] The ECHO was reviewed and interpreted by medically qualified personnel and the results and any abnormalities were recorded.

### *9.5.4 Pharmacokinetics*

Single blood samples for PK determinations were drawn at 5 ± 2 min after the end of study drug administration at baseline (Week 1), Week 24, and Week 25. In addition, blood samples for PK determination were drawn pre-administration [redacted] and post-administration at 5, 15, 30, 60, and 90 min and 2, 4, 6, 8, 12, and 24 hours after the end of study drug administration at Week 12. Urine was collected within 30 min prior to dosing and for 24 hours after the end of dosing at the Week 12 visit only.

Plasma and urine samples were analyzed to determine eteplirsen concentrations using a validated anion exchange high-performance liquid chromatography with fluorescence detection bioanalytical method. The range of detection of the assay in plasma was 10-1000 ng/mL using a sample size of 100 µL. The range of detection of the assay in urine was 25-2500 µg/mL using a sample size of 100 µL.

### *9.5.5 Appropriateness of Measurements*

The efficacy of eteplirsen was evaluated by examining its ability to increase the expression of dystrophin protein. Dystrophin expression is typically measured using Western blot and/or analysis of dystrophin intensity and the percentage of dystrophin-positive fibers via IHC. While all 3 methods are semi-quantitative, measurement of the percentage of dystrophin-positive fibers also allows for confirmation that newly made dystrophin is correctly localized to the sarcolemma membrane and yields data about dystrophin expression on a cell-by-cell basis. This information is not available in Western blotting, which involves homogenizing a large piece of tissue and analyzing overall protein levels using controls as semiquantitative comparators. In addition, Western blot has very limited utility in quantification at the low and high detection limits, whereas IHC based methods are more reliable in these ranges. While measurement of dystrophin intensity using IHC permits visual inspection of dystrophin localization, localization is not represented in the actual analysis.

Because analysis of the percentage of dystrophin-positive fibers provides the most information and requires substantially less sample material than non-IHC methods, it was used to determine

eteplirsen's effect on dystrophin expression in this study. Analyses of dystrophin intensity (via IHC) and dytrophin protein levels (via Western blot) were conducted to support those results, and RT-PCR was performed to detect the presence of appropriate length mRNA in muscle samples and confirm exon skipping. Three different anti-dystrophin antibodies were used for the IHC assays (MANDYS106, DYS2, and DYS3) and 2 were used for the Western blot assay (MANDYS106 and DYS2). As MANDYS106 is believed to yield the most sensitive and reproducible results in the field of dystrophin research, results obtained using this antibody are considered primary. In addition, CD3, CD4, and CD8 cell counts were measured in muscle samples taken at baseline and after 12 or 24 weeks of treatment [redacted]

[redacted]

The clinical effects of eteplirsen were evaluated using several validated measures, including the 6MWT and the NSAA. Performance on the 6MWT reflects the global status of all systems involved in walking, including the neuromuscular, pulmonary, and cardiovascular systems (Takeuchi 2008). Based on precedent in other neuromuscular disorders (Kierkegaard 2007, van der Ploeg 2010), the 6MWT is appropriate for assessing ambulatory ability in boys with DMD and a change in performance on the 6MWT represents a clinically meaningful endpoint. Of note, the 6MWT has been previously used in DMD patients and is feasible, accurate, and reproducible in the target population (McDonald 2010a, McDonald 2010b). Like the 6MWT, the NSAA is considered a reliable and valid measure of functional ability in DMD (Mayhew 2011).

[redacted]

[redacted]

Pulmonary function testing was performed because progressive weakening of the respiratory muscles over time leads to pulmonary complications, which are one of the main causes of morbidity and mortality in DMD. As the patients in this study were all less than 13 years of age and were expected to have near normal PFT results at baseline, changes in pulmonary function were not anticipated over the 24-week period assessed in this study. However, continued treatment with eteplirsen in the extension study (4658-us-202) could help elucidate potential effects of eteplirsen on pulmonary function.

The safety assessments performed during this study, including monitoring for AEs, physical examinations, vital signs, and clinical safety laboratory testing, are standard measurements

conducted to ensure the safety of patients. ECGs and ECHOs were performed to ensure the safety of participants and also in light of known cardiac complications secondary to the underlying disease. Although no renal effects of eteplirsen have been observed in clinical studies conducted to date, nontoxic accumulation of basophilic material in the kidneys was observed in primates and in mice in preclinical studies. Therefore, kidney functioning was carefully monitored via regular assessments of serum cystatin C and urine cystatin C and KIM-1.

## 9.6 Data Quality Assurance

Training regarding the specifics of the protocol, study drug, data collection procedures, and ICH GCP guidelines was provided for key study personnel at the site initiation visit and on an as needed basis thereafter. In addition, study manuals that included specifics regarding the handling and shipping of specimens, contact information for Sponsor study personnel, and detailed instructions for specific study procedures were provided.

The study site monitor periodically inspected the eCRFs and paper diaries/questionnaires, study documents, and research facilities associated with the study to ensure the accuracy and completeness of the data recorded on the eCRFs; to ensure that all protocol requirements, applicable regulations, and the Investigator's obligations were fulfilled; and to resolve any inconsistencies in the study records. A 100% check of the eCRF data against the source documents was performed during these visits.

Data Management was initially performed by [redacted] (CRO), according to their written standard operating procedures (SOPs). Designated study personnel entered patient data via a secure, web-based server into eCRFs. Initially, during the data collection process, representatives of [redacted] used automated quality control programs to identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Electronic queries for data clarification or correction were forwarded to the site for resolution. PharPoint Research, Inc. assumed responsibility of data management five months prior to database lock. [redacted] created all initial documentation and performed all processes prior to PharPoint Research, Inc. When all patient data were deemed cleaned and all electronic queries were resolved, the principal Investigator approved and electronically signed the eCRFs at the study site. Close out activities for the study were performed by PharPoint Research, Inc. per their SOPs.

Sarepta performed independent quality assurance audits of the study site and contract research organizations, and the CRO performed an internal audit of the clinical study database. These activities are detailed within the audit certificate provided in [redacted]

## 9.7 Statistical Methods

All available data were included in data listings. No imputation of values for missing data was performed. Placebo-treated patients were pooled for the purpose of inferential statistical analyses.

Summary statistics consisted of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD) or, as appropriate, the standard error of the mean (SE), minimum, and maximum values for continuous variables.

Baseline for all quantitative safety measures (laboratory parameters, vital signs, and 12-lead ECG measurements) were defined as the last valid evaluation done before the study drug administration on Week 1.

A copy of the statistical analysis plan (SAP) is provided in [redacted]

### *9.7.1 Analysis Populations*

The following analysis populations were defined:

- Safety Population: included all randomized patients who received any amount of study drug. Analyses performed on the safety population were done according to the treatment actually received.
- Full Analysis Population: the same as the safety population. Given the small sample size, analyses performed on the full analysis population were done according to the treatment actually received.
- Modified Intent-to-Treat Population (mITT): The mITT is similar to the Full Analysis Population but excluded 2 patients who showed rapid disease progression during the first few weeks of this study.
- PK Population: included all randomized patients for whom there were adequate PK samples from which to estimate PK parameters. Analyses performed on the PK samples were done according to the treatment actually received.

### *9.7.2 Study Patients*

#### *9.7.2.1 Patient Disposition*

Patient disposition was summarized with frequency count and percentage of the following items: patients who were randomized, who received study medication (safety population), and who discontinued early. The reasons for discontinuation were to be summarized for all enrolled patients. Patient disposition and patient eligibility (including inclusion/exclusion criteria) are presented in data listings.

#### *9.7.2.2 Protocol Deviations*

A listing of protocol deviations based on the blinded review of the study data prior to database lock is provided. The listing describes the nature of the deviation (e.g., inclusion/exclusion, prohibited therapies) and indicates whether the Sponsor or Principal Investigator permitted the deviation.

#### *9.7.2.3 Demography*

Demographic characteristics including age, sex, race, ethnicity, and baseline characteristics including genetic mutation, height, weight, and body mass index (BMI) were summarized by treatment and overall. Demographic data and baseline characteristics are presented in the data listings.

#### *9.7.2.4 Medical History*

Medical history was coded using MedDRA version 14.1. Medical history data are listed.

#### *9.7.2.5 Prior and Concomitant Medications*

A prior medication was defined as any medication taken prior to the first study drug administration. A concomitant medication was defined as any medication taken after the first study drug administration. Prior and concomitant medications were coded using the current version of the World Health Organization classification for therapeutic class and drug name (WHO Drug Dictionary Enhanced).

All medications, whether prior or concomitant, appear in the data listings; concomitant medications were summarized by drug classification and preferred term, displaying the number and percentage of patients per treatment group.

#### *9.7.2.6 Treatment Compliance and Extent of Exposure*

Study drug exposure was characterized by calculating, for each patient, the total amount of medication taken during the study and the time in days between the first dose and the last.

The cumulative exposure, total volume of drug administered, and the total number of infusions received were summarized by treatment group. Dosing information is provided in a listing.

### *9.7.3 Efficacy Analysis Methods*

Testing and summary statistics of all efficacy endpoints combined placebo patients in Groups 3a and 3b into a single group.

For the purpose of the efficacy analyses, and as appropriate based on the Schedule of Events, baseline was defined as the maximum observed value on Day 1 or Day 2 at Visit 1; Week 12 was defined as the maximum observed value on Day 1 or Day 2 at Visit 13; and Week 24 was defined as the maximum observed value on Day 1 or Day 2 at Visit 25. If data for any 1 visit day was missing, then the non-missing value from the same visit was used.

#### *9.7.3.1 Primary Efficacy Endpoint*

The primary efficacy endpoint was the change from baseline in the percentage of dystrophin-positive fibers as measured in muscle tissue using IHC at Week 12 for patients who received 50 mg/kg/wk eteplirsen and at Week 24 for patients who received 30 mg/kg/wk eteplirsen vs. placebo.

The primary efficacy endpoint was analyzed by comparing the 50 mg/kg/wk eteplirsen treatment group (Group 1) at Week 12 to the combined placebo treatment group (Groups 3a and 3b), and the 30 mg/kg/wk eteplirsen treatment group (Group 2) at Week 24 to the combined placebo treatment group using the change from baseline values. An analysis of covariance (ANCOVA) for ranked data was used for these analyses with baseline values and duration of DMD as covariates.

[redacted]

### 9.7.3.2 Biopsy-Related Efficacy Endpoints

Additional biopsy-related endpoints included change from baseline to Week 12 for Groups 1 and 3a and to Week 24 for Groups 2 and 3b in:

- dystrophin intensity levels as measured by IHC
- dystrophin protein levels as measured by Western blot analysis
- exon skipping as measured by RT-PCR
- CD3, CD4, and CD8 lymphocyte counts as measured by IHC

Dystrophin intensity levels and dystrophin protein levels were summarized by time point (baseline, on-treatment) and treatment group (placebo, 30 mg/kg/wk eteplirsen, 50 mg/kg/wk eteplirsen, combined eteplirsen group). These summaries included descriptive statistics for the observed, on-treatment change from baseline, and the percentage of on-treatment change from baseline values. No inferential testing of these parameters was performed.

[redacted]

Exon skipping data were summarized using the number and percentage of patients with either no evidence of exon skipping or evidence of skipping exon 51 on RT-PCR. No inferential testing of this parameter was performed.

### 9.7.3.3 Functional Efficacy Endpoints and Health-Related Quality of Life

Functional efficacy endpoints included change from baseline to week 24 in the:

- 6MWT
- Timed 4-Step Test
- MVICT
- NSAA total score, and NSAA components including the Timed 10-Meter Run and Rise Time
- 9-Hole Peg Test
- PFT including FVC, %FVC, $FEV_1$, $\%FEV_1$, $FEV_1$/FVC ratio; MIP, and MEP

Change from baseline to week 24 on the PedsQL, including the NMM, was an additional endpoint.

Analysis of change from baseline to Week 24 in the 6MWT, Timed 4-Step Test, MVICT, NSAA total score, and the Timed 10-Meter Run was based on a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) with treatment (placebo, 30 mg/kg/wk, 50 mg/kg/wk), time, and treatment-by-time interaction terms as fixed effects, patient nested within treatment as a random effect, and with the baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix was used. The treatment comparison was made between each of the active treatments and placebo at Week 24 and at each of the other post-baseline visits. This procedure did not replace missing data, all available on-treatment assessments were used in the mixed model. In this analysis, in which the MMRM is fitted to all post-baseline data, patients in the full analysis population who did not have complete data still contributed to the estimates at Week 24, but had less weight in the analysis than those patients with complete data. An analysis of observed scores available at each visit was also performed. Estimates for changes from baseline at each time-point in each treatment group and for treatment difference were provided with 95% confidence intervals (CIs) and p-values using the least significant difference contrasts from the model. The same MMRM analysis described above was repeated to compare the combined eteplirsen group to placebo.

Sensitivity analyses of each of the clinical assessment parameters were to be performed and included an analysis of covariance for repeated measures (ANCOVAR) model with treatment, time, and treatment-by-time interaction terms as fixed effects, patient nested within treatment as a random effect, and with baseline values and time since DMD diagnosis as covariates. In this analysis, patients without a post-baseline value had a value imputed from an earlier post-baseline score using the last-observation-carried-forward (LOCF) method (baseline values will not be carried forward).

If there was strong evidence suggesting that any of these endpoints deviated from normal distribution, as judged by the p-value for the Shapiro-Wilk test, then ANCOVA for ranked data (Stokes 2000) was utilized.

The data for the NSAA Rise Time, and time to complete the 9-Hole Peg Test using dominant hand were analyzed using the MMRM analysis described above.

All remaining discrete functional outcome variables, which include components of the NSAA and the 9-Hole Peg Test, were summarized with descriptive statistics by treatment group and visit. Week 24 data was also compared to baseline data using the Cochran-Mantel Haenszel (CMH) statistics or other cross-tabulation procedures as appropriate based on the distribution of the observed data.

Pulmonary function testing parameters including FVC, %FVC, $FEV_1$, $\%FEV_1$, $FEV_1$/FVC ratio, MIP, and MEP were summarized using descriptive statistics by treatment group (placebo, 30 mg/kg/wk eteplirsen, 50 mg/kg/wk eteplirsen, combined eteplirsen group) and visit using the observed, on-treatment change from baseline, and the percentage of on-treatment change from baseline. The MMRM analysis described above was also utilized for these data.

[redacted]

[redacted]

### *9.7.4 Safety Analysis Methods*

The safety and tolerability of eteplirsen was assessed through a review and evaluation of:

- the frequency and severity of AEs, SAEs, and discontinuations due to AEs
- Safety laboratory tests including hematology, coagulation, and serum chemistry assays (including serum cystatin C) and urinalysis (including urinary cystatin C and KIM-1)
- Immune response to dystrophin (ELISPOT)
- Vital signs
- Physical examinations
- 12-lead ECGs
- ECHOs

#### *9.7.4.1 Adverse Events*

Adverse events were coded using MedDRA (version 14.1) and are reported by primary system, organ, class (SOC) and primary term (PT). Only TEAEs are summarized; non-emergent events are only recorded in the patient listings. For all AE tables, the number and percentage of patients reporting AEs, grouped by MedDRA SOC and PT, are summarized by treatment groups.

Multiple occurrences of the same AE (at the PT level) in the same patient are counted only once in the frequency tables. If a patient experienced multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to study drug was used to summarize AEs by relationship and severity.

#### *9.7.4.2 Laboratory Measurements*

Descriptive statistics for continuous hematology, clinical chemistry, urinalysis and coagulation laboratory measurements are presented by treatment group and time point. Summary statistics for each lab parameter and time point, as well as the change from baseline to that time point are displayed, and a shift table comparing the number and percentage of low, normal, and high status of the lab values at baseline to Week 24 is presented.

The following are also provided:

- A list of the laboratory's normal ranges and units used for the predefined change (PC) values, and the definitions of clinically significant laboratory values
- A table of frequencies of predefined change abnormal (PCA) increases and PCA decreases
- A list of all clinically significant abnormal laboratory findings, if applicable

ELISPOT results are summarized by time point (baseline, Weeks 6, 12, 18, and 24) and treatment group (placebo, 30 mg/kg/wk eteplirsen, 50 mg/kg/wk eteplirsen, combined eteplirsen group). These summaries include descriptive statistics for the observed, on-treatment change from baseline, and the percentage of on-treatment change from baseline values.

#### *9.7.4.3 Vital Signs*

Vital signs parameters are presented by treatment group and time point, summarizing the actual values and change from baseline to each on-treatment time point using descriptive statistics. Vital signs data are presented in the data listings. The following are also provided:

- A table of frequencies of PCA increases and decreases
- A list of all clinically significant abnormal vital sign findings, if applicable
- A list of all vital signs per patient; values that exceeded the normal range, satisfied PCA criteria, and were clinically significant were flagged as shown in the table below.

#### *9.7.4.4 12-Lead ECGs*

Electrocardiogram results are presented by treatment group and time point, summarizing the actual values and change from baseline to each on-treatment time point using descriptive statistics. Results are also presented in a listing. In addition, a shift table comparing N (%) of ECG status at baseline to Week 24, a table of frequencies of PCA increases and decreases (see Table 9-6:), and a list of all clinically significant abnormal ECG findings vs. baseline recordings, if applicable, are also provided.

[redacted]

#### *9.7.4.5 Echocardiograms*

The actual value and change from baseline to each on-treatment time point are summarized by treatment group for each ECHO for ejection fraction (EF) and shortening fraction (SF). All of the ECHO parameters are listed by patient in a data listing.

#### *9.7.4.6 Holter Monitoring*

Holter monitoring results are provided in a data listing.

#### *9.7.4.7 Physical Examinations*

Physical examination results are provided in a data listing.

### *9.7.5 Pharmacokinetic Analysis Methods*

Pharmacokinetic parameters estimated from plasma concentration-time data, using actual sampling times, included:

| | |
|---|---|
| $C_{max}$ | observed maximum plasma concentration (ng/mL) |
| $T_{max}$ | time to reach the observed maximum plasma concentration (h) |
| $AUC_{last}$ | (also referred to as $AUC_{0\text{-}last}$) area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration $C_{last}$ (ng.h/mL) |
| $AUC_{0\text{-}24}$ | area under the plasma concentration-time curve from time 0 to 24 hours post infusion |
| $AUC_{\infty}$ | (also referred to as $AUC_{0\text{-}\infty}$) area under the plasma concentration-time curve from time 0 to infinite time, calculated according to the following equation $AUC = AUC_{last} + C_{last} / \lambda_z$ (ng.h/mL) |
| MRT | mean residence time, calculated as $AUMC_{\infty}/AUC_{\infty}$. $AUMC_{\infty}$ is the area under the first moment curve |
| $\%AUC_{\infty,ex}$ | (also referred to as AUC% ext) percentage of $AUC_{\infty}$ obtained by extrapolation, calculated by the following equation: |

$$\frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}} * 100$$

| | |
|---|---|
| $t_{1/2,\lambda}$ | (also referred to as $t_{1/2}$) elimination half-life associated with the terminal slope ($\lambda_z$) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$ |
| $\lambda_z$ | first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve |
| $C_{max,ss}$ | maximum plasma concentration during a dosing interval at steady state |
| $C_{trough}$ | trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose |
| $C_{avg,ss}$ | average plasma concentration at steady-state, calculated as $AUC\tau/\tau$ |
| CL/F | (also referred to as $CL_{PL}$) total clearance of drug after extravascular administration, uncorrected for absolute bioavailability, calculated as: $D/AUC\tau$ |
| $V_{dss}$ | (also referred to as $V_{ss}$) apparent volume of distribution at steady-state, calculated as MRT*CL |

In addition, the following PK parameters were calculated, whenever possible, for each patient based on the urine eteplirsen concentrations:

| | |
|---|---|
| $A_e$ | amount of unchanged drug excreted in urine |
| $CL_R$ | renal clearance, where $CL_R = A_e/AUC_{0-24}$ |
| % Excreted | the percentage excreted, where % Excreted = $100*(A_e/dose)$ |

The PK analysis was performed by Combs Consulting Service, Mountain View, CA, USA.

Data were listed for all patients with available plasma and/or urine concentrations per treatment. All concentrations below the limit of quantification (BLQ) or missing data were labeled as such in the concentration data listings. Concentrations BLQ were treated as 0 in the summary statistics and for the calculation of PK parameters.

Pharmacokinetic parameters for eteplirsen were calculated using non-compartmental analysis. Actual sampling times were used in all final PK analyses. Per protocol sampling times were used to calculate mean plasma concentrations for graphical displays.

$C_{max}$ and $T_{max}$ were taken directly from the data. The elimination rate constant, $\lambda z$, was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The range of data used for each patient and dose was determined by visual inspection of a semi-logarithmic plot of concentration vs. time.

Listing of individual patient plasma and urine concentrations, actual blood sampling times, and PK parameters and graphs of concentration vs. time were prepared by dose group. Plasma

concentrations and PK parameters were summarized by and compared among dose groups using descriptive statistics.

Dose proportionality for $C_{max}$ and AUC(s) were assessed visually by plotting these parameters (original and dose-normalized) against dose. Further statistical analysis could be performed to assess dose proportionality.

Pharmacokinetic parameters were computed using the software WinNonlin 5.2 or WinNonlin 6.1-Phoenix (both from Pharsight Corp. Mountain View, CA. USA). Plots were prepared using SigmaPlot 11.0 or higher (Systat Software, Inc. San Jose, CA. USA) or Prism 5 or higher (GraphPad Software, Inc. La Jolla, CA. USA).

### *9.7.6 Determination of Sample Size*

[redacted] A sample size of 12 total patients was selected with 4 patients in each of the 3 treatment groups: 50 mg/kg/wk eteplirsen, 30 mg/kg/wk eteplirsen, and placebo. This sample size was selected to provide an assessment of the response to these doses, background variability, and the proposed methods of assessing treatment effect.

### *9.7.7 Interim Analyses and Data Monitoring*

The DSMB performed a blinded interim safety analysis to evaluate the safety of all treated patients after the patients in Groups 1 and 3a completed the Week 12 muscle biopsy. The DSMB convened again to evaluate the study experience and safety of all treated patients once the remaining patients in groups 2 and 3b completed the Week 24 muscle biopsy. No safety concerns were identified by the DSMB at any point during the conduct of the study and the study was completed without interruption.

### *9.7.8 Reporting of Study Results from weeks 25 through 28*

All data collected after Week 24 through Week 28, including AEs, concomitant medications and therapies, vital signs and weight, physical examinations, safety laboratory assessments, PK, and dosing information, are presented in data listings.

### *9.7.9 Changes in the Conduct of the Study or Planned Analyses*

#### *9.7.9.1 Changes in the Conduct of the Study*

Protocol 4658-us-201was amended 7 times. The original protocol, Version 1, was finalized 24 September 2010; however, patients were not enrolled into the study until Version 3, dated 25 May 2011 was implemented. The version number of each protocol amendment, the date each was issued, and the substantive changes to the study enacted with each amendment are summarized below.

**Version 2 (Amendment 1), 21 April 2011**

- 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 patients from 5 patients each in 4 groups to 4 patients 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 patient enrollment from 5 to 15 years of age to 7 to 13 years of age.
- Added the requirement that patients be able to walk between 200 and 350 meters on the 6MWT to the entry criteria.
- Changed the entry requirement that participants be on a stable dose of corticosteroids for at least 12 weeks before study entry to at least 24 weeks before study entry.

[redacted]

- Added several assessments including the NSAA, PedsQL, the 9-Hole Peg Test, inflammatory biomarkers (CD3, CD4, and CD8 in muscle biopsies), MIP and MEP, and removed the timed 4-Step Test and the DEXA.
- Added post-treatment muscle biopsies to the list of required assessments.
- Specified that the primary efficacy endpoint would be dystrophin production.

**Version 3 (Amendment 2), 25 May 2011**

[redacted]

- Added the Timed 4-Step Test to the efficacy assessments.
- Expanded the maximum distance on the 6MWT inclusion criterion from 350 to 400 meter.
- [redacted]

**Version 4.0 (Amendment 3), 22 June 2011**

[redacted]

**Version 5.0 (Amendment 4), 10 August 2011**

- Clarified that the 6MWT would be administered twice during the screening visit and that the mean of the 2 assessments ± 10% of the lower or upper limit (200 m, 400 m) would be the value used to determine qualification.

- Specified that the screening Holter monitor recording would be reviewed prior to the patient undergoing a muscle biopsy, and that if the average heart rate during the recording exceeded 100 bpm, the patient would either be started on β-blockers and rescreened in 4 weeks or excluded from the study.

[redacted]

- Added the DSMB to the protocol.

**Version 6.0 (Amendment 5), 8 September 2011**

- Clarified that MIP and MEP would be measured, not % predicted MIP and MEP.

[redacted]

- Deleted the 24-hour total urine protein collection from the protocol, because the results from the initial collection were confounded by the presence of nitrogen in eteplirsen.

**Version 7.0 (Amendment 6), 04 November 2011**

[redacted]

- Made the 6MWT a secondary endpoint.
- Modified the statistical method to the Wilcoxon rank-sum test, because it was more appropriate for the sample size of this study.

[redacted]

- 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.

[redacted]

- Updated planned statistical analyses.
- Removed the "modified intent to treat" and "per protocol" populations from the list of analysis populations and added a "full analysis population", which, like the safety population, included all patients who received any study medication.

**Version 8.0 (Amendment 7), 07 January 2012**

- Extended the duration of the study from 24 to 28 weeks.
- Specified that beginning Week 25, patients who received placebo for the first 24 weeks of the study would begin receiving the same dose of eteplirsen to which they were placebo-matched while those who received 50 or 30 mg/kg/wk eteplirsen for the first 24 weeks would continue to receive the same dose regimen of eteplirsen without interruption.

[redacted]

### *9.7.9.2 Changes in the Planned Analyses*

Changes made to the planned analyses are described below:

- A modified intent-to-treat (mITT) population was evaluated that matched the full analysis population but excluded 2 patients (Patients 009, 010) randomized to 30mg/kg/wk eteplirsen who showed signs of rapid disease progression within weeks after enrollment and were unable to perform measures of ambulation at or beyond 24 weeks.

- For the purpose of the efficacy analyses of functional endpoints, the maximum observed value of any 2 consecutive days of assessment was to be used in the analysis. As the intent for this plan was to use the patient's best score as a reflection of best effort made, the minimum value (representing best value) was used for the following assessments: the Timed 10-meter run and Rise Time from the NSAA.

[redacted]

- Specific conditions for the Western blot and RT-PCR analyses were altered after the initial analyses were performed because of higher than expected concentrations in total protein and RNA extracted from the tissue samples, respectively. Results from the initial and follow-up analyses are included in the summary tables and listings. Results from the follow-up analyses are reported in the body of this study report.

[redacted]

- A single blood sample for PK determination was drawn at 5 ± 2 minutes after the end of study drug administration at Week 1. However, these samples were lost during shipping and therefore, were not available for analysis.

# 10 STUDY PATIENTS

## 10.1 Disposition of Patients

A total of 12 patients were randomized into the groups shown below:

**Table 10-1: Treatment Groups**

| Group | Treatment/Dose of Eteplirsen | N |
|---|---|---|
| 1 | 50 mg/kg/wk eteplirsen for 28 weeks | 4 |
| 2 | 30 mg/kg/wk eteplirsen for 28 weeks | 4 |
| 3a | Placebo once weekly for 24 weeks then 50 mg/kg/wk eteplirsen for 4 weeks | 2 |
| 3b | Placebo once weekly for 24 weeks then 30 mg/kg/wk eteplirsen for 4 weeks | 2 |

All 12 patients received all scheduled infusions of study medication and completed the study as planned. Patient disposition is summarized by group in [redacted], while randomization assignments and disposition are presented by patient in [redacted], respectively.

## 10.2 Protocol Deviations

All patients had at least 1 protocol deviation during the conduct of this study ([redacted]. All patients met all inclusion and exclusion criteria with the exception of 2 patients in the 30 mg/kg/wk eteplirsen group, Patients 009 and 010, who did not meet inclusion criterion 4, which required patients to have been on a stable dose of corticosteroids and other medications for at least 24 weeks before entering the study. Both of these patients began receiving carvedilol (i.e., beta blocker) and losartan (i.e., angiotensin II antagonist) 21.5 weeks prior to screening (in addition to ongoing treatment with prednisone since 2007). All other protocol deviations were considered minor and were not expected to have affected the conduct of the study, the quality of the data, or the interpretation of the findings.

## 10.3 Demographic and Other Baseline Characteristics

### *10.3.1 Demographic Characteristics*

Patients were recruited for this study nationwide across the US. Enrolled patients resided in 10 different states (CA, VA, IL, FL, PA, WI, MO, NY, NC, and NH).

All patients were male and, except for one patient of Asian descent, all were white. At baseline, patients had a mean age of 8.8 years, a mean height of 123.7 centimeters (cm), a mean weight of 31.5 kg, and a mean body mass index (BMI) of 20.4 kg/m$^2$. Compared to the other groups, patients in the 30 mg/kg/wk group were slightly older, heavier, and taller at baseline (Table 10-2), and they achieved a shorter distance on the 6MWT (Table 10-3).

**Table 10-2: Summary of Demographic Characteristics (Safety Population)**

| Parameter | | Placebo N = 4 | Eteplirsen 30 mg/kg/wk N = 4 | Eteplirsen 50 mg/kg/wk N = 4 | Eteplirsen All Eteplirsen N = 8 | All Patients N = 12 |
|---|---|---|---|---|---|---|
| **Gender n(%)** | Male | 4 (100) | 4 (100) | 4 (100) | 8 (100) | 12 (100) |
| **Age, years** | Mean | 8.5 | 9.3 | 8.5 | 8.9 | 8.8 |
| | Median | 8.5 | 9.0 | 8.5 | 9.0 | 9.0 |
| | SD | 1.73 | 0.50 | 1.29 | 0.99 | 1.22 |
| | Min, Max | 7, 10 | 9, 10 | 7, 10 | 7, 10 | 7, 10 |
| **Height, cm** | Mean | 119.3 | 130.5 | 121.3 | 125.9 | 123.7 |
| | Median | 118.5 | 133.5 | 117.5 | 124.5 | 118.5 |
| | SD | 3.40 | 9.47 | 7.85 | 9.45 | 8.40 |
| | Min, Max | 116, 124 | 117, 138 | 117, 133 | 117, 138 | 116, 138 |
| **Weight, kg** | Mean | 30.65 | 34.85 | 29.05 | 31.95 | 31.52 |
| | Median | 32.15 | 37.40 | 27.10 | 31.25 | 32.15 |
| | SD | 6.035 | 7.050 | 6.376 | 6.952 | 6.411 |
| | Min, Max | 22.1, 36.2 | 24.8, 39.8 | 23.7, 38.3 | 23.7, 39.8 | 22.1, 39.8 |
| **BMI, kg/m$^2$** | Mean | 21.51 | 20.23 | 19.57 | 19.90 | 20.44 |
| | Median | 22.02 | 20.68 | 19.80 | 20.23 | 20.47 |
| | SD | 3.980 | 1.470 | 1.918 | 1.622 | 2.573 |
| | Min, Max | 16.4, 25.6 | 18.1, 21.5 | 17.0, 21.7 | 17.0, 21.7 | 16.4, 25.6 |
| **Race, n(%)** | Asian | 0 | 1 (25) | 0 | 1 (12.5) | 1 (8.3) |
| | White | 4 (100) | 3 (75) | 4 (100) | 7 (87.5) | 11 (91.7) |

Source: Table 14.1.2
Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation.

Demography and other baseline characteristics are summarized by treatment group in Table 14.1.2 and presented by patient in Listing 16.2.4.1.

### *10.3.2 Other Baseline Characteristics*

As shown in [redacted], the majority of patients had deletions in exons 49-50 (41.7%) or 45-50 (25%) of the dystrophin gene, though patients with deletions in exons 48-50, 50, and 52 were also included. On average, patients had been diagnosed with DMD for 56.4 months (or 4.7 years) at the start of the study.

With respect to cardiac status, ECHOs ([redacted]) and Holter monitor testing ([redacted]) performed during the screening period did not reveal any abnormalities in any of the patients; however, 8 patients showed evidence of left, right, or biventricular hypertrophy

on the screening ECG ([redacted]). This was assessed as not clinically significant in all cases and was expected given the patients' age and diagnosis.

In terms of walking ability and endurance, mean distances walked on the 6MWT at baseline ([redacted]) were similar to those reported in other studies of children with DMD (Mazzone, 2010; McDonald, 2010a), and as expected, were well below the 600 plus meters typically observed in healthy children of similar ages (Geiger, 2007; Li, 2007). Respiratory function as measured by %FVC and %$FEV_1$ was within normal limits ([redacted]).

A review of medical history data ([redacted]) indicated that 8 of 12 patients had resolved or active medical conditions at study entry. The most common ongoing medical condition was allergies (in 3 patients), but ongoing and/or prior gastrointestinal complaints were not uncommon.

## Table 10-3: Baseline Disease Characteristics (Safety Population)

| Parameter | | Placebo N = 4 | Eteplirsen 30 mg/kg/wk N = 4 | Eteplirsen 50 mg/kg/wk N = 4 | All Eteplirsen N = 8 | All Patients N = 12 |
|---|---|---|---|---|---|---|
| **Mutation** | 45-50 n (%) | 0 | 2 (50) | 1 (25) | 3 (37.5) | 3 (25) |
| | 48-50 n (%) | 0 | 1 (25) | 0 | 1 (12.5) | 1 (8.3) |
| | 49-50 n (%) | 3 (75) | 0 | 2 (50) | 2 (25) | 5 (41.7) |
| | 50 n (%) | 1 (25) | 0 | 0 | 0 | 1 (8.3) |
| | 52 n (%) | 0 | 1 (25) | 1 (25) | 2 (25) | 2 (16.7) |
| **Time Since DMD Diagnosis, months** | Mean | 50.3 | 52.5 | 66.5 | 59.5 | 56.4 |
| | Median | 51.0 | 57.0 | 68.0 | 57.0 | 57.0 |
| | SD | 13.74 | 14.06 | 44.29 | 31.33 | 26.40 |
| | Min, Max | 36, 63 | 32, 64 | 18, 112 | 18, 112 | 18, 112 |
| **Duration of Steroid Use, months** | Mean | 44.875 | 49.875 | 52.825 | 51.350 | 49.192 |
| | Median | 45.550 | 53.800 | 52.050 | 53.800 | 53.800 |
| | SD | 21.6297 | 13.4812 | 35.3952 | 24.8455 | 23.0344 |
| | Min, Max | 21.7, 66.7 | 30.4, 61.5 | 15.5, 91.7 | 15.5, 91.7 | 15.5, 91.7 |
| **Holter Monitor Average Heart Rate, bpm** | Mean | 96.8 | 96.8 | 93.8 | 95.2 | 95.8 |
| | Min, Max | 91, 102 | 86, 102 | 86, 102 | 86, 102 | 86, 102 |
| **6MWT[a], meters** | Mean | 394.5 | 355.3 | 396.0 | 375.6 | |
| | Median | 379.0 | 359.0 | 395.0 | 380.5 | |
| | SD | 42.25 | 74.78 | 26.61 | 56.34 | |
| | Min, Max | 364, 456 | 261, 442 | 365, 429 | 261, 442 | |
| **%$FEV_1$ (%)** | Mean | 111.000 | 92.750 | 94.000 | 93.375 | |
| | Median | 109.500 | 92.000 | 98.500 | 95.500 | |
| | SD | 11.9722 | 7.7190 | 23.2236 | 16.0351 | |
| | Min, Max | 98, 127 | 85, 102 | 62, 117 | 62, 117 | |
| **%FVC (L)** | Mean | 116.3 | 95.3 | 92.3 | 93.8 | |
| | Median | 119.0 | 98.0 | 88.0 | 93.5 | |
| | SD | 15.44 | 7.80 | 11.59 | 9.29 | |
| | Min, Max | 96, 131 | 84, 101 | 84, 109 | 84, 109 | |

Sources: Table 14.1.2 (mutations and time from DMD diagnosis to screening); Listing 16.2.8.5 (24-hour Holter Monitor findings at screening); [redacted] (6MWT results); [redacted] (PFT results); [redacted] (Duration of steroid use at baseline).

6MWT results are maximum observed value of 2 tests administered on 2 consecutive days at screening.

**Abbreviations**: 6MWT = 6-Minute Walk Test; %FEV1 = percent predicted forced expiratory volume in 1 second; %FVC = percent predicted forced vital capacity; bpm = beats per minute; DMD = Duchenne muscular dystrophy; max = maximum; min = minimum; SD = standard deviation.

## 10.4 Treatment Compliance and Extent of Exposure

Study drug was administered by authorized personnel at the study site. All 12 patients received all 28 infusions of study drug as planned ([redacted]).

[redacted]

Exposure to study drug through the first 24 weeks of this study is summarized by group in [redacted], while exposure to study drug through week 28 is presented by patient in [redacted]

# 11 EFFICACY EVALUATION

Results of efficacy assessments through Week 24 for the full analysis and mITT populations are presented in the following sections. Efficacy was not assessed during Weeks 25 through 28.

## 11.1 Data Sets Analyzed

Efficacy analyses were performed using the full analysis population, which included all 12 patients. In addition, some efficacy analyses were repeated using an mITT population that excluded 2 patients in the 30mg/kg/wk eteplirsen group (Patients 009 and 010) who showed signs of rapid disease progression within weeks of enrollment resulting in extreme scores on all measures of functional mobility by week 8 and the inability to perform measures of ambulation at or beyond 24 weeks.

Safety analyses were performed using the safety population, which included all 12 patients.

Pharmacokinetic analyses were performed using the PK population, which included all 12 patients.

## 11.2 Primary Efficacy Endpoint-Change from Baseline in the Percentage of Dystrophin-Positive Fibers

Once weekly treatment with 30 mg/kg eteplirsen for 24 weeks significantly increased the mean percentage of dystrophin-positive muscle fibers (assessed via IHC using anti-dystrophin antibody MANDYS106) in DMD patients compared to placebo ($p \leq 0.002$; [redacted]). Thus, the study met the pre-specified primary efficacy comparison for a difference between placebo- and eteplirsen-treated patients in the percentage of dystrophin-positive fibers.

As shown in [redacted], patients treated with 30 mg/kg/wk eteplirsen demonstrated a substantial increase in the mean percentage of dystrophin positive fibers from a baseline of 18.9% of normal to 41% of normal at Week 24. In contrast, there were no mean increases in the percentage of dystrophin positive fibers in placebo treated patients biopsied at Weeks 12 or 24. There were also no mean increases from baseline in the 50 mg/kg/wk eteplirsen treated patients biopsied at Week 12, suggesting that eteplirsen-induced increases in the percentage of dystrophin-positive fibers are more dependent on duration of treatment rather than administered dose.

**Table 11-1: Effect of Eteplirsen on Dystrophin-Positive Fibers Detected by IHC with MANDYS106 (Full Analysis Population)[a]**

| Time point | | Placebo N = 4 | 30 mg/kg/wk Eteplirsen N = 4 | 50 mg/kg/wk Eteplirsen N = 4 |
|---|---|---|---|---|
| **Baseline** | Mean | 15.64 | 18.19 | 11.00 |
| | Median | 15.58 | 17.80 | 11.51 |
| | SD (SE) | 10.742 (5.371) | 5.501 (2.751) | 4.668 (2.334) |
| | Min, Max | 3.2, 28.2 | 11.9, 25.3 | 5.4, 15.6 |
| **On-Treatment[b]** | Mean | 11.59 | 41.14 | 11.79 |
| | Median | 9.44 | 38.77 | 11.81 |
| | SD (SE) | 7.130 (3.565) | 10.097 (5.049) | 4.456 (2.228) |
| | Min, Max | 5.7, 21.7 | 32.7, 54.3 | 6.4, 17.2 |
| **Change from Baseline** | Mean | -4.05 | 22.95[c] | 0.79 |
| | Median | -6.13 | 23.46 | 2.52 |
| | SD (SE) | 5.834 (2.917) | 5.792 (2.896) | 7.099 (3.549) |
| | Min, Max | -8.5, 4.5 | 15.9, 29.0 | -9.3, 7.4 |

Source: [redacted]

[a]Results are expressed as a percentage of total fibers counted. As normal muscle samples have 100% dystrophin-positive muscle fibers, percent total dystrophin-positive muscle fibers can also be expressed as a percentage of normal.

[b]On-treatment samples are from Week 12 for all 4 patients in the 50 mg/kg/wk eteplirsen group and 2 patients in the placebo group, or from Week 24 for all 4 patients in the 30 mg/kg/wk eteplirsen group and 2 patients in the placebo group.

[c] p = 0.002 for 30 mg/kg/wk eteplirsen vs. placebo based on ANCOVA model for ranked data with treatment (placebo, 30 mg/kg/wk, 50 mg/kg/wk) as a fixed effect and baseline value and time since DMD diagnosis as covariates.

**Abbreviations**: max = maximum; min = minimum; SD = standard deviation; SE = standard error.

[redacted] summarizes the percentage of dystrophin-positive fibers assessed via IHC using the anti-dystrophin antibodies MANDYS106, Dys2, and Dys3 by treatment group, while statistical analyses of these data are summarized in [redacted]. The by-patient listing of dystrophin-positive fiber counts is provided in [redacted]

## 11.3 Biopsy-Related Efficacy Endpoints

### *11.3.1 Change from Baseline in Dystrophin Intensity Levels*

Once weekly treatment with 50 mg/kg eteplirsen for 12 weeks or with 30 mg/kg eteplirsen for 24 weeks appeared to increase mean dystrophin fiber intensity (assessed via IHC using MANDYS106 and expressed as a percentage of normal control levels) to a greater degree than placebo ([redacted]). No inferential statistical analysis was planned for this endpoint.

[redacted] and [redacted] summarize dystrophin intensity levels and change from baseline assessed via IHC using the MANDYS106 and Dys2 antibodies. Dystrophin intensity levels are presented by patient in [redacted]

### *11.3.2 Change from Baseline in Total Dystrophin Protein Levels*

Consistent with its effects on the percentage of dystrophin-positive fibers [redacted] treatment with 30 mg/kg/wk eteplirsen for 24 weeks appeared to increase the mean total amount of dystrophin protein in muscle tissue homogenates (as measured by Western blot using MANDYS106 and expressed as a percentage of normal control levels) more than either placebo or 50 mg/kg/wk eteplirsen administered for 12 weeks [redacted]. No inferential statistical analysis was planned for this endpoint.

**Table 11-3: Effect of Eteplirsen on Dystrophin Protein as Measured by Western Blot (Full Analysis Population)[a]**

| Time point | | Placebo N = 4 | 30 mg/kg/wk Eteplirsen N = 4 | 50 mg/kg/wk Eteplirsen N = 4 |
|---|---|---|---|---|
| **Baseline** | Mean | 0.38 | 0.17 | 0.15 |
| | Median | 0.39 | 0.15 | 0.05 |
| | SD (SE) | 0.157 (0.079) | 0.197 (0.099) | 0.243 (0.121) |
| | Min, Max | 0.2, 0.5 | 0.0, 0.4 | 0.0, 0.5 |
| **On-Treatment[b]** | Mean | 0.45 | 2.02 | 0.59 |
| | Median | 0.44 | 1.03 | 0.21 |
| | SD (SE) | 0.170 (0.085) | 2.708 (1.354) | 0.841 (0.420) |
| | Min, Max | 0.3, 0.7 | 0.1, 6.0 | 0.1, 1.8 |
| **Change from Baseline** | Mean | 0.07 | 1.86 | 0.44 |
| | Median | 0.05 | 0.69 | 0.20 |
| | SD (SE) | 0.315 (0.157) | 2.801 (1.401) | 0.916 (0.458) |
| | Min, Max | -0.3, 0.5 | 0.1, 6.0 | -0.4, 1.7 |

Source: [redacted]
[a]Results are expressed as a percentage of normal.
[b]On-treatment samples are from Week 12 for all 4 patients in the 50 mg/kg/wk eteplirsen group and 2 patients in the placebo group, and from Week 24 for all 4 patients in the 30 mg/kg/wk eteplirsen group and 2 patients in the placebo group.
**Abbreviations**: max = maximum; min = minimum; SD = standard deviation; SE = standard error.

[redacted] summarizes dystrophin protein levels assessed by Western blot analysis using the MANDYS106 and the Dys2 antibodies. The by-patient listing of dystrophin protein levels is provided in [redacted].

[redacted]

There were no statistically significant differences between the treatment groups in the change from baseline in CD3, CD4, or CD8 levels. [redacted]

There were also no statistically significant differences between the treatment groups in the change from baseline in MHC1 or MHC2 levels. [redacted]

### *11.3.4 Exon Skipping*

Exon skipping, determined by comparing results of RT-PCR testing of muscle homogenates in samples taken at screening to those taken at Weeks 12 (for Groups 1 and 3a) or 24 (for Groups 2

and 3b), is summarized in [redacted] As expected, there was no evidence of exon skipping in any of the treatment groups at screening or in the placebo-treated patients at any time point. In contrast, exon skipping was observed in all 4 of the 50 mg/kg/wk eteplirsen patients biopsied at Week 12 and all 4 of the 30 mg/kg/wk eteplirsen patients biopsied at Week 24.

[redacted]

Results of the exon-skipping analysis are summarized by treatment group in [redacted] and presented by patient in [redacted]

## 11.4 Functional Efficacy Endpoints

As specified in [redacted], functional endpoint data were analyzed using the MMRM. Data were analyzed using an ANCOVA of ranked data when assumptions of normality were violated.

### *11.4.1 Change from Baseline in 6MWT*

The change from baseline in 6MWT scores varied across patients with some showing improvement, others remaining relatively stable, and still others showing marked decline [redacted]

As shown in [redacted] from baseline to Week 24, placebo-treated patients experienced a mean decline of 17.3 meters, while patients in the 30 and 50 mg/kg/wk eteplirsen groups showed mean declines of 134.8 and 2.3 meters, respectively. The large decline in the 30 mg/kg/wk eteplirsen group was directly attributable to Patients 009 and 010; when these 2 patients were excluded from the analysis, the mean change from baseline to Week 24 was a decline of 12.5 meters.

As the assumptions of normality were violated for the full analysis population, the ANCOVA of ranked data was used to compare the 2 eteplirsen treatment groups to placebo. This analysis showed no significant differences between the treatment groups [redacted]. For the mITT population, the assumptions of normality were not violated and the MMRM analysis also showed no significant differences between the treatment groups [redacted].

**Table 11-5: Summary and Change from Baseline in 6MWT Results (Full Analysis and mITT Populations)**

| Time point | Placebo (N = 4) | 30 mg/kg/wk (N = 4) | 30 mg/kg/wk (mITT)[a] (N = 2) | 50 mg/kg/wk (N = 4) |
|---|---|---|---|---|
| **Baseline[b]** | | | | |
| **Mean** | 394.5 | 355.3 | 407.0 | 396.0 |
| **Median** | 379.0 | 359.0 | 407.0 | 395.0 |
| **SD (SE)** | 42.25 (21.12) | 74.78 (37.39) | 49.50 (35.00) | 26.61 (13.30) |
| **Min, Max** | 364, 456 | 261, 442 | 372, 442 | 365, 429 |
| **Week 24[b]** | | | | |
| **Mean** | 377.3 | 220.5 | 394.5 | 393.8 |
| **Median** | 377.5 | 204.0 | 394.5 | 403.5 |
| **SD (SE)** | 19.00 (9.50) | 203.14 (101.57) | 51.62 (36.50) | 53.67 (26.84) |
| **Min, Max** | 354, 400 | 43, 431 | 358, 431 | 325, 443 |
| **Change at Week 24** | | | | |
| **Mean** | -17.3 | -134.8 | -12.5 | -2.3 |
| **Median** | -12.0 | -116.0 | -12.5 | 1.5 |
| **SD (SE)** | 28.06 (14.03) | 144.71 (72.36) | 2.12 (1.50) | 29.89 (14.95) |
| **Min, Max** | -56, 11 | -296, -11 | -14, -11 | -40, 28 |

Source: [redacted]

[a] mITT excludes Patients 009 and 010.

[b] 6MWT value for each patient is the maximum distance achieved on days 1 and 2.

**Abbreviations**: 6MWT = 6-Minute Walk Test; max = maximum; min = minimum; mITT = modified intent to treat population; SD = standard deviation; SE = standard error.

Performance on the 6MWT at baseline and over time, and change from baseline over time is summarized by treatment group for the full analysis population in [redacted], and for the mITT in [redacted]. Results of statistical analyses and supporting documentation for the full analysis population are summarized in [redacted], [redacted], and [redacted]. Results of statistical analyses and supporting documentation for the mITT population are summarized in [redacted] and [redacted] Performance on the 6MWT at baseline and over time is presented by patient in [redacted]

[redacted]

**Table 11-6: Summary and Change from Baseline in Timed 4-Step Test (Full Analysis and mITT Populations)**

| Time point | Placebo (N = 4) | 30 mg/kg/wk (N = 4) | 30 mg/kg/wk (mITT)[a] (N = 2) | 50 mg/kg/wk (N = 4) |
|---|---|---|---|---|
| **Baseline**[b] | | | | |
| **Mean** | 5.30 | 4.88 | 3.75 | 3.50 |
| **Median** | 4.35 | 4.80 | 3.75 | 3.35 |
| **SD (SE)** | 1.934(0.967) | 1.355(0.677) | 0.354(0.250) | 1.074(0.537) |
| **Min, Max** | 4.3, 8.2 | 3.5, 6.4 | 3.5, 4.0 | 2.4, 4.9 |
| **Week 24**[c] | | | | |
| **Mean** | 4.08 | 14.73 | 3.70 | 3.35 |
| **Median** | 4.15 | 10.15 | 3.70 | 3.15 |
| **SD (SE)** | 0.685(0.342) | 15.069(7.535) | 0.990(0.700) | 1.240(0.620) |
| **Min, Max** | 3.3, 4.7 | 3.0, 35.6 | 3.0, 4.4 | 2.1, 5.0 |
| **Change at Week 24** | | | | |
| **Mean** | -1.22 | 9.85 | -0.05 | -0.15 |
| **Median** | -0.80 | 5.35 | -0.05 | -0.05 |
| **SD (SE)** | 1.597(0.798) | 13.797(6.898) | 0.636(0.450) | 1.115(0.558) |
| **Min, Max** | -3.5, 0.2 | -0.5, 29.2 | -0.5, 0.4 | -1.6, 1.1 |

Source: [redacted]

[a] mITT excludes patients 009 and 010.

[b] Baseline is the last non-missing value before first dose.

[c] Week 24 is the best time achieved on days 1 and 2 of that visit.

**Abbreviations**: max = maximum; min = minimum; mITT = modified intent to treat population; SD = standard deviation; SE = standard error.

Performance on the Timed 4-Step Test at baseline and over time, and change from baseline over time is summarized by treatment group for the full analysis population in [redacted], and for the mITT in [redacted]. Results of statistical analyses and supporting documentation for the full analysis population are summarized in [redacted], and Table 14.2.6.2.3. Results of statistical analyses and supporting documentation for the mITT population are summarized in [redacted] Performance on the Timed 4-Step Test at baseline and over time is presented by patient in [redacted]

[redacted]

[redacted]

### *11.4.4 Change from Baseline in the North Star Ambulatory Assessment Total Score*

While individual performance on the NSAA varied considerably ([redacted], mean NSAA scores were relatively stable from baseline to Week 24 in the placebo and 50 mg/kg/wk eteplirsen groups [redacted]. In contrast, mean scores decreased noticeably in the 30 mg/kg/wk eteplirsen group due to the performance of Patients 009 and 010. When these 2 patients were excluded, the mean change from baseline to Week 24 for the 30 mg/kg/wk eteplirsen group was 1 point.

An MMRM analysis of the full analysis population revealed statistically significant differences between the placebo and 30 mg/kg/wk groups in favor of placebo at Week 24 [redacted]. When the same analysis was performed on the mITT population, a statistically significant difference between the placebo and 50 mg/kg/wk eteplirsen groups, in favor of placebo, was detected at Week 24 [redacted].

**Table 11-7: Summary and Change from Baseline in NSAA Total Scores (Full Analysis and mITT Populations)**

| Time point | Placebo (N = 4) | 30 mg/kg/wk (N = 4) | 30 mg/kg/wk (mITT)[a] (N = 2) | 50 mg/kg/wk (N = 4) |
|---|---|---|---|---|
| **Baseline[b]** | | | | |
| **Mean** | 23.3 | 20.8 | 22.5 | 29.0 |
| **Median** | 22.0 | 19.0 | 22.5 | 29.0 |
| **SD (SE)** | 3.30 (1.65) | 5.19 (2.59) | 7.78 (5.50) | 2.31 (1.15) |
| **Min, Max** | 21, 28 | 17, 28 | 17, 28 | 27, 31 |
| **Week 24[c]** | | | | |
| **Mean** | 26.5 | 14.8 | 23.5 | 26.8 |
| **Median** | 26.5 | 13.5 | 23.5 | 27.0 |
| **SD (SE)** | 4.04 (2.02) | 10.53 (5.27) | 4.95 (3.50) | 5.12 (2.56) |
| **Min, Max** | 23, 30 | 5, 27 | 20, 27 | 21, 32 |
| **Change at Week 24** | | | | |
| **Mean** | 3.3 | -6.0 | 1.0 | -2.3 |
| **Median** | 2.0 | -5.5 | 1.0 | -2.0 |
| **SD (SE)** | 2.50 (1.25) | 8.60 (4.30) | 2.83 (2.00) | 2.99 (1.49) |
| **Min, Max** | 2, 7 | -16, 3 | -1, 3 | -6, 1 |

Source: [redacted]

[a] mITT excludes patients 009 and 010.

[b] Baseline is the last non-missing value before first dose.

[c] Week 24 is the best score achieved on days 1 and 2 of that visit.

**Abbreviations**: max = maximum; min = minimum; mITT = modified intent to treat population; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SE = standard error.

Performance on the NSAA at baseline and over time, and change from baseline over time is summarized by treatment group for the full analysis population in [redacted], and for the mITT in [redacted]. Results of statistical analyses and supporting documentation for the

full analysis population are summarized in [redacted], [redacted], and [redacted]. Results of statistical analyses and supporting documentation for the mITT population are summarized in [redacted]
Performance on the NSAA at baseline and over time is presented by patient in [redacted]

[redacted]

### *11.4.6 Change from Baseline in Rise-Time*

Rise time (a component of the NSAA) scores were variable across patients and over time [redacted] While mean times increased noticeably from baseline to Week 24 in the 30 mg/kg/wk eteplirsen group, this was again due to the performance of Patients 009 and 010 [redacted]. When these 2 patients were excluded, the mean time to rise from the floor decreased by 3 seconds.

No statistically significant differences between the treatment groups were detected for the full analysis [redacted] or mITT [redacted] populations when the results were analyzed using an ANCOVA of ranked data.

**Table 11-9: Summary and Change from Baseline in Rise Time (Full Analysis and mITT Populations)**

| Time point | Placebo (N = 4) | 30 mg/kg/wk (N = 4) | 30 mg/kg/wk (mITT)[a] (N = 2) | 50 mg/kg/wk (N = 4) |
|---|---|---|---|---|
| **Baseline**[b] | | | | |
| **Mean** | 6.63 | 8.55 | 7.60 | 5.73 |
| **Median** | 6.30 | 9.15 | 7.60 | 3.90 |
| **SD (SE)** | 1.360(0.680) | 4.576(2.288) | 6.223(4.400) | 4.213(2.106) |
| **Min, Max** | 5.4, 8.5 | 3.2, 12.7 | 3.2, 12.0 | 3.1, 12.0 |
| **Week 24**[c] | | | | |
| **Mean** | 5.93 | 14.25 | 4.50 | 10.28 |
| **Median** | 5.45 | 11.55 | 4.50 | 3.50 |
| **SD (SE)** | 1.632(0.816) | 12.479(6.239) | 1.556(1.100) | 13.822(6.911) |
| **Min, Max** | 4.6, 8.2 | 3.4, 30.5 | 3.4, 5.6 | 3.1, 31.0 |
| **Change at Week 24** | | | | |
| **Mean** | -0.70 | 5.70 | -3.10 | 4.55 |
| **Median** | -0.65 | 5.70 | -3.10 | -0.20 |
| **SD (SE)** | 1.140(0.570) | 10.852(5.426) | 4.667(3.300) | 9.635(4.818) |
| **Min, Max** | -2.1, 0.6 | -6.4, 17.8 | -6.4, 0.2 | -0.4, 19.0 |

Source: Table 14.2.2.1, Table A.14.2.2.1

[a] mITT excludes patients 009 and 010.

[b] Baseline is the last non-missing value before first dose.

[c] Week 24 is the best time achieved on days 1 and 2 of that visit.

**Abbreviations**: max = maximum; min = minimum; mITT = modified intent to treat population; SD = standard deviation; SE = standard error.

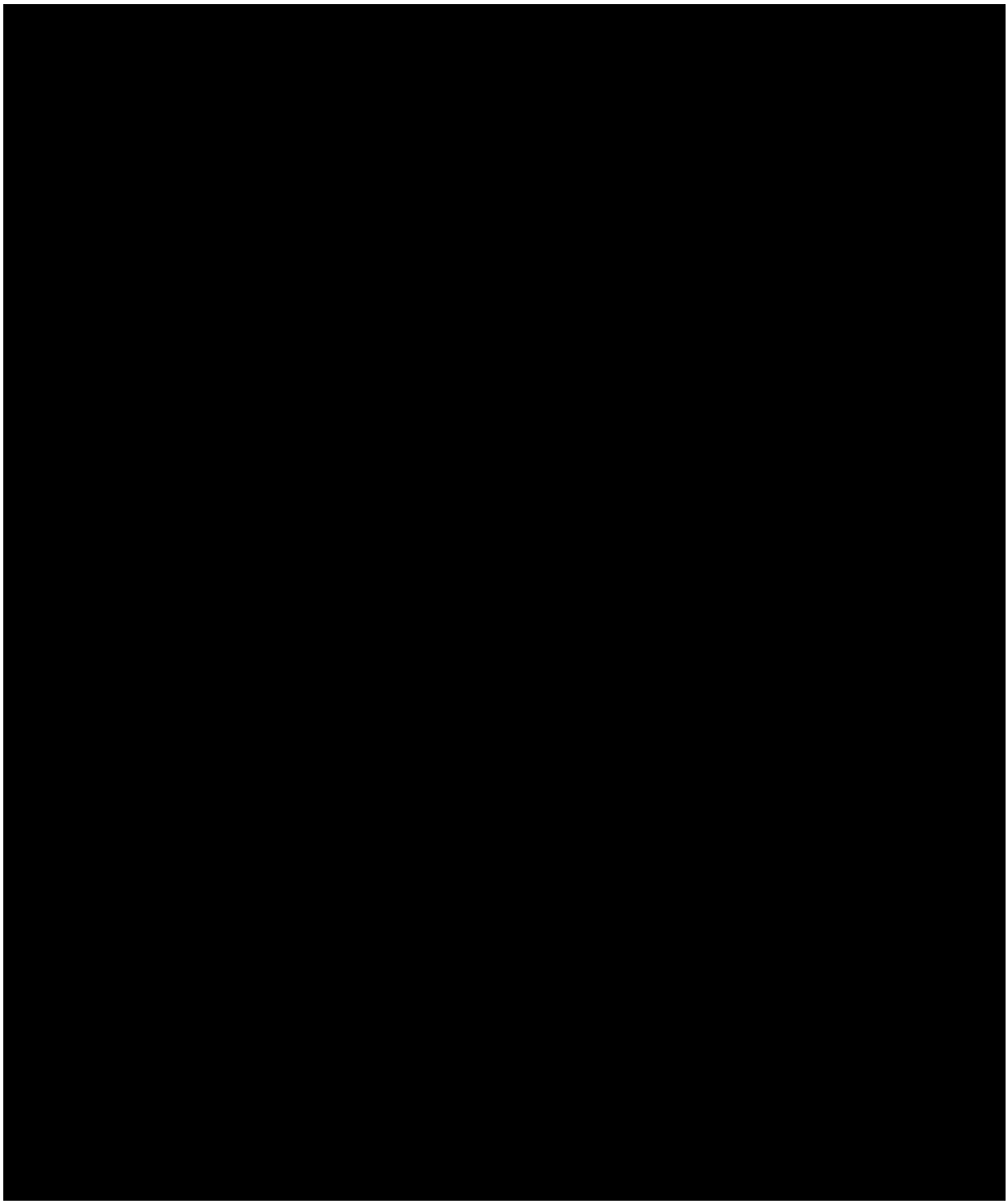
[redacted]

[redacted]

[redacted]

### *11.4.8 Change from Baseline on Pulmonary Function Test Measurements*

[redacted]



[redacted]

Pulmonary function test results at baseline and over time, and change from baseline over time are summarized by treatment group for the full analysis population in [redacted]. Results of statistical analyses and supporting documentation for the full analysis population are summarized in [redacted] Pulmonary function test results at baseline and over time are presented by patient in [redacted]

[redacted]

[redacted]

## 11.5 Statistical /Analytical Issues

Other than the changes discussed in Section 9.7.9.2, there were no statistical or analytical issues for this study.

## 11.6 Summary of Efficacy Findings

- Once weekly treatment with 30 mg/kg eteplirsen for 24 weeks significantly increased the mean percentage of dystrophin-positive muscle fibers in DMD-treated patients compared to placebo ($p \leq 0.002$) to meet the study's pre-specified primary efficacy endpoint.

- Patients treated with 30 mg/kg/wk eteplirsen demonstrated an increase from baseline in the mean percentage of dystrophin-positive fibers to 41.1% of normal at Week 24. In contrast, there were no detectable increases from baseline in the mean percentage of dystrophin-positive fibers in placebo-treated patients biopsied at Weeks 12 or 24. There were also no detectable mean increases from baseline in patients treated with the higher dose of 50 mg/kg/wk and biopsied at Week 12.

[redacted]

- Consistent with its effects on the percentage of dystrophin-positive fibers, treatment with 30 mg/kg/wk eteplirsen for 24 weeks appeared to increase the mean total amount of dystrophin protein more than placebo or 50 mg/kg/wk eteplirsen for 12 weeks as measured in muscle tissue homogenates using Western blot.

- Exon skipping was confirmed for all eteplirsen-treated patients in both dose groups.

- Performance on measures involving ambulation including the 6MWT, Timed 4-Step Test, and several components of the NSAA, was highly variable with some patients showing minor improvements from baseline, most remaining stable, and 2 patients in the 30 mg/kg/wk eteplirsen group showing marked decline within weeks of the first dose.

When those 2 patients were excluded from the analyses of these measures (mITT analyses), there were no meaningful differences between the groups.

- Changes in other functional efficacy endpoints including the MVICT, 9-Hole Peg Test, and PFT were generally small with no clear differentiation observed between the eteplirsen and placebo groups.

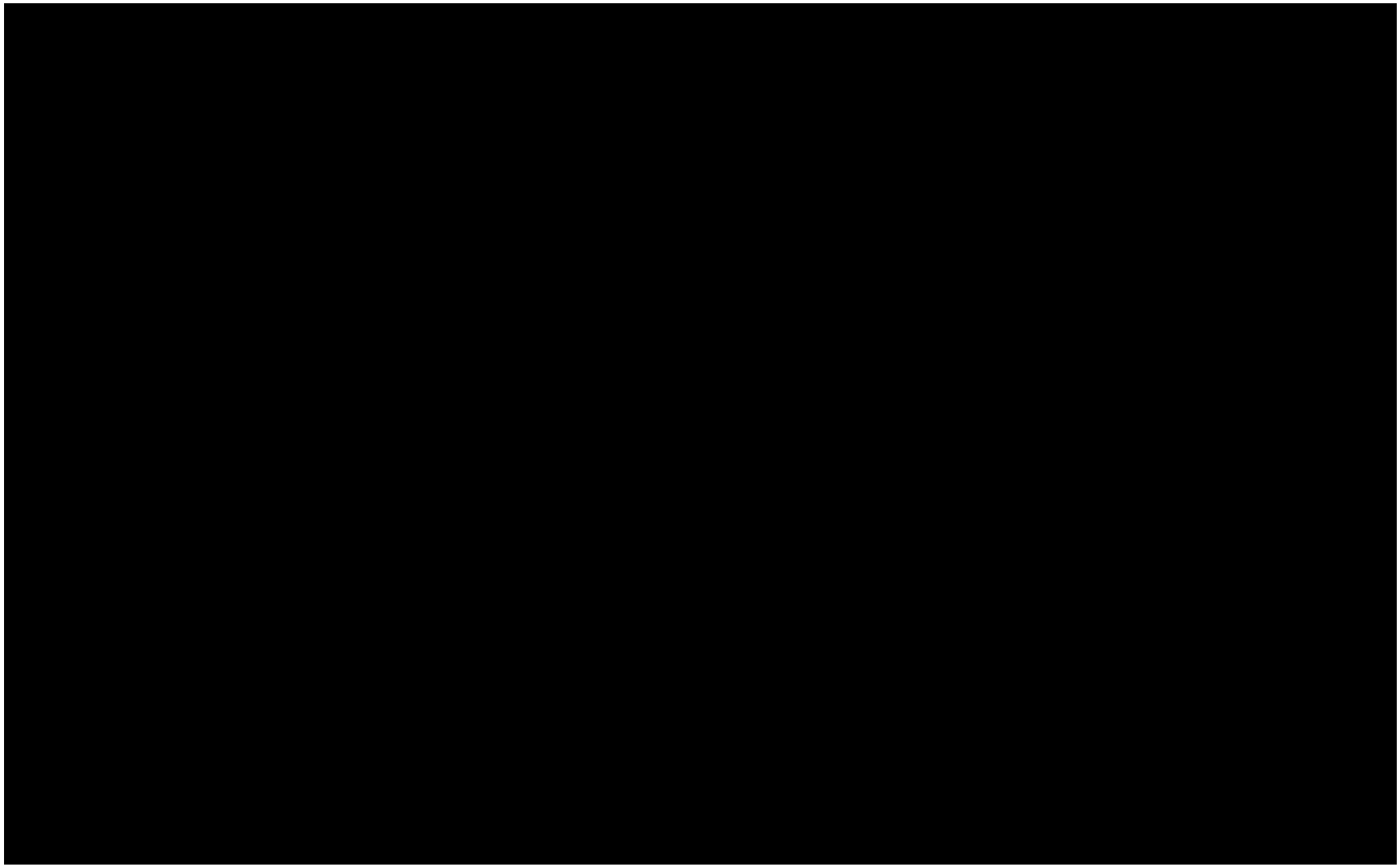
## 11.7 Pharmacokinetic Evaluation

A single blood sample for PK determination was drawn at 5 ± 2 minutes after the end of study drug administration at Week 1. However, these samples were lost during shipping and therefore, were not available for analysis. At Week 12, all concentrations for eteplirsen-treated patients were above the limit of quantification at 24 hours post-end of infusion. [redacted] Thus, 5-minute concentrations were approximately proportional to dose in that the ratio of mean concentrations at 50 vs. 30 mg/kg/wk was 1.56, which is comparable to the dose ratio of 50/30 or 1.67. Concentrations were similar across Weeks 12 through 25 as shown by the average of the concentration ratios which were 1.024 and 1.254 for the 30 and 50 mg/kg/wk dose levels, respectively.

Analysis of PK parameters at Week 12 ([redacted]) showed that, as expected, $T_{max}$ occurred at the first time point post-end of infusion (i.e., 5 minutes after the end of the 60-minute infusion). $C_{max}$ averaged 77,200 ± 15,568 ng/mL for 30 mg/kg/wk and 124,600 ± 54,898 ng/mL for 50 mg/kg/wk. Variability in $C_{max}$, $AUC_{0-\infty}$, $AUC_{0-last}$ and $AUC_{0-24}$ was about 20% (coefficient of variation, CV%) for 30 mg/kg/wk and about 50% for 50 mg/kg/wk. $C_{max}$ at 50 mg/kg/wk was 1.61 times that at 30 mg/kg/wk and $AUC_{0-\infty}$ at 50 mg/kg/wk was 1.99 that at 30 mg/kg/wk. Thus, between these 2 dose levels, $C_{max}$ appeared to increase proportionally with dose increment, whereas $AUC_{0-\infty}$ increased in a greater than proportional manner with dose.

With respect to urinary excretion and renal clearance, 24-hour collection concentrations for placebo-treated patients were all below the limits of quantification. Results from analysis of the 24-hour collections in eteplirsen-treated patients ([redacted]) showed that 95.5 ± 63.9% of the dose was excreted at the 30 mg/kg/wk dose level and 69.4 ± 24.7% at the 50 mg/kg/wk dose level. The average percentage of dose excreted at the 30 mg/kg/wk was high due to 1 value of 190% of dose excreted, which was considered erroneous as no reason for this anomaly is known. Excluding this value, the percent excreted averaged 64.1 ± 13.8%. Renal clearance averaged 221 ± 53.5 mL/hr/kg (excluding the anomalous value) and 234 ± 154 mL/hr/kg for the 30 and 50 mg/kg/wk dose levels, respectively. Thus, renal clearance of drug accounted for about 64.1% and 69.5% of total systemic clearance ($CL_{PL}$) for the 2 dose groups, respectively.

Sampling times for collection of plasma and urine samples are presented by patient in [redacted] and [redacted], respectively. The complete PK report is provided in [redacted].



## Table 11-13: Urinary Excretion and Renal Clearance for Eteplirsen At Week 12

| Treatment Group | Patient | Body Weight (kg) [a] | Urine Volume (mL) | Urine Concentration (µg/mL) | Amount Excreted (mg) | Percent of Dose Excreted | $CL_R$ (mL/hr/kg) | $CL_{PL}$ (mL/hr/kg) | Percent $CL_R/CL_{PL}$ |
|---|---|---|---|---|---|---|---|---|---|
| **Eteplirsen 30 mg/kg/wk** | 002 | 25.5 | 1,587 | 278 | 441 | 57.7 | 261 | 453 | 57.7 |
| | 006 | 36.1 | 1,220 | 485 | 592 | 54.6 | 161 | 293 | 54.8 |
| | 009 | 44.7 | 1,620 | 661 | 1,071 | 79.9 | 242 | 302 | 80.0 |
| | 010 | 44.2 | 2,555 | 985 | 2,517 | 190 | 588 | 309 | 190 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Mean | 37.6 | 1,746 | 602 | 1,155 | 95.5 | 313 | 339 | 95.6 |
| | SD | 9.0 | 569 | 299 | 947 | 63.9 | 189 | 75.8 | 63.9 |
| | CV% | 23.9 | 32.6 | 49.7 | 81.9 | 66.9 | 60.2 | 22.3 | 66.9 |
| **Eteplirsen 50 mg/kg/wk** | 003 | 24.5 | 600 | 1,920 | 1,152 | 94.0 | 438 | 465 | 94.2 |
| | 004 | 29.3 | 460 | 1,350 | 621 | 42.4 | 147 | 346 | 42.5 |
| | 012 | 42.5 | 1,024 | 1,140 | 1,167 | 54.9 | 89.3 | 162 | 55.1 |
| | 015 | 27.0 | 1,058 | 1,100 | 1,164 | 86.2 | 263 | 305 | 86.3 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Mean | 30.8 | 786 | 1,378 | 1,026 | 69.4 | 234 | 319 | 69.5 |
| | SD | 8.0 | 301 | 378 | 270 | 24.7 | 154 | 125 | 24.7 |
| | CV% | 26.0 | 38.3 | 27.4 | 26.3 | 35.6 | 65.7 | 39.1 | 35.5 |

Source: [redacted]

**Note**: In the PK report in [redacted], patient numbers are preceded by the number "1", for example Patient 002 is identified as Patient 1002.

**Note**: The amount excreted for Patient 010 is greater than the dose given and therefore percent of dose excreted and relative clearance is greater than 100%. This impacts the mean values for this dose level. The reason for this anomaly is not known.

**Abbreviations**: $CL_{PL}$ = total clearance of drug after extravascular administration; $CL_R$ = renal clearance

## 11.8 Summary of Pharmacokinetic Findings

- Plasma concentrations at 5 minutes post end of infusion were similar between 12 and 24 weeks on active drug for each dose level.
- Between the 30 and 50 mg/kg/wk dose levels, $C_{max}$ increased in a manner proportional with dose, wheareas AUC increased in a somewhat greater than proportional manner.
- $CL_{PL}$, $V_{ss,}$ and half-life were similar at both dose levels.
- Given eteplirsen's half-life of about 3 hours, and the rapid decline in concentrations over 24 hours, little if any accumulation would be expected upon repeated once-weekly dosing of eteplirsen.
- Renal clearance of intact eteplirsen accounted for approximately two-thirds of total systemic clearance.
- The PK profile of eteplirsen given as a 1-hour IV infusion was similar to that previously reported in the DMD patient population in study AVI-4658-28.

# 12 SAFETY EVALUATION

Safety results are summarized by treatment group through the end of the placebo-controlled treatment period (Week 24). Safety results through Week 28 are presented by patient in the data listings. AE data are presented through Week 28 in [redacted] below.

## 12.1 Prior and Concomitant Medications

The most commonly reported types of medications administered during this study included: topical anesthetics (for infusions, blood draws, and injections, n = 12), anilides (for pain, n = 8), glucocorticoids (for DMD, n = 12), and benzodiazepine derivatives, opioid anesthetics, or other general anesthetics (for muscle biopsies, n = 12). Seventy-five percent of patients also received Vitamin D supplements (n = 9).

Concomitant medications are summarized by group in [redacted] and presented by patient in [redacted]

## 12.2 Adverse Events

### *12.2.1 Brief Summary of Adverse Events*

The 12 patients in this study experienced a total of 112 AEs from the time of informed consent through Week 28, 99 (88%) of which were treatment-emergent [redacted]). A summary of AEs occurring from the time of informed consent through Week 24 is provided in Table 12-1. All TEAEs were assessed as unrelated to study drug except for 1 case of nausea, reported by a placebo patient and assessed as possibly/probably related to study drug. All TEAEs were assessed as mild or moderate in severity except for 1 case of severe nasal congestion reported by a 30 mg/kg/wk eteplirsen patient and 1 case each of severe bone pain and severe loss of balance reported by a 30 mg/kg/wk eteplirsen patient. There were no-treatment-related or severe TEAEs reported during the last 4 weeks of this study when all patients were receiving 30 or 50 mg/kg/wk eteplirsen.

No SAEs, discontinuations, or deaths were reported during this study.

**Table 12-1: Overview of Adverse Events Through Week 24 (Safety Population)**

| Adverse Event Categories | Placebo N=4 n(%) | Eteplirsen 30 mg/kg/wk N=4 n(%) | Eteplirsen 50 mg/kg/wk N=4 n(%) | Eteplirsen All Eteplirsen N=8 n(%) | All Patients N=12 n(%) |
|---|---|---|---|---|---|
| **Patients with pre-treatment AEs**[a] | 4 (100) | 3 (75) | 4 (100) | 7 (88) | 11 (92) |
| **Patients with TEAEs**[b] | 4 (100) | 4 (100) | 4 (100) | 8 (100) | 12 (100) |
| **Patients with Treatment-Related TEAEs** | 1 (25) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) |
| **Patients with Mild TEAEs**[c] | 2 (50) | 0 | 4 (100) | 4 (50) | 6 (50) |
| **Patients with Moderate TEAEs**[c] | 2 (50) | 2 (50) | 0 | 2 (25) | 4 (33.3) |
| **Patients with Severe TEAEs**[c] | 0 | 2 (50) | 0 | 2 (25) | 2 (16.7) |
| **Patients who discontinued due to AEs** | 0 | 0 | 0 | 0 | 0 |
| **Patients with SAEs** | 0 | 0 | 0 | 0 | 0 |
| **Deaths** | 0 | 0 | 0 | 0 | 0 |

Source: [redacted]

[a] Pre-treatment AEs are AEs that began after signing the informed consent form and before the first administration of study drug.

[b] TEAEs are AEs that started during or after the first administration of study drug or started before the first infusion of study drug but worsened in severity.

[c]Worst severity in case of multiple occurrences per preferred term.

**Abbreviations**: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

### *12.2.2 All Adverse Events*

Most of the TEAEs that occurred during this study could be traced to the muscle biopsies that were required of all patients, the underlying disease of DMD, and the young age of the participants (Table 12-2). Thus, the most commonly reported types of TEAEs through Week 24 included: procedural pain, occurring in 7 (58%) of the 12 patients; oropharyngeal pain and [redacted] and cough and extremity pain, both occurring in 4 (33%) patients. A review of all TEAEs by SOC did not show any increases in the frequency of events in any SOC in eteplirsen-treated patients vs. placebo-treated patients or with increasing dose of eteplirsen.

The most commonly reported TEAEs in all patients through week 28 were consistent with those reported through week 24, and included: procedural pain and oropharyngeal pain each occurring in 7 (56%) patients; [redacted]; and cough, nasal congestion, and extremity pain each occurring in 4 (33%) patients.

## Table 12-2: Summary of Treatment-Emergent Adverse Events Through Week 24 (Safety Population)

| Body System/ Preferred Term | Placebo N = 4 n(%) | Eteplirsen 30 mg/kg/wk N = 4 n(%) | Eteplirsen 50 mg/kg/wk N = 4 n(%) | Eteplirsen All Eteplirsen N = 8 n(%) | All Patients[a] N = 12 n(%) |
|---|---|---|---|---|---|
| **At Least One TEAE** | 4 (100.0) | 4 (100.0) | 4 (100.0) | 8 (100.0) | 12 (100.0) |
| **Injury, poisoning & procedural complications** | 4 (100.0) | 3 (75.0) | 4 (100.0) | 7 (87.5) | 11 (91.7) |
| Procedural pain | 3 (75.0) | 1 (25.0) | 3 (75.0) | 4 (50) | 7 (58.3) |
| Fall | 1 (25.0) | 1 (25.0) | 0 | 1 (12.5) | 2 (16.7) |
| Incision site pain | 1 (25.0) | 1 (25.0) | 0 | 1 (12.5) | 2 (16.7) |
| Arthropod bite | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Back injury | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Foot fracture | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| Joint injury | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Wound dehiscence | 1 (25.0) | 0 | 0 | 0 | 1 ( 8.3) |
| **Respiratory, thoracic & mediastinal disorders** | 3 (75.0) | 4 (100.0) | 1 (25.0) | 5 (62.5) | 8 (66.7) |
| Oropharyngeal pain | 3 (75.0) | 3 (75.0) | 0 | 3 (37.5) | 6 (50) |
| Cough | 2 (50) | 1 (25.0) | 1 (25.0) | 2 (25.0) | 4 (33.3) |
| Nasal congestion | 2 (50) | 1 (25.0) | 0 | 1 (12.5) | 3 (25.0) |
| Sinus congestion | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Upper respiratory tract congestion | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| **Musculoskeletal & connective tissue disorders** | 3 (75.0) | 2 (50) | 2 (50) | 4 (50) | 7 (58.3) |
| Pain in extremity | 3 (75.0) | 0 | 1 (25.0) | 1 (12.5) | 4 (33.3) |
| Back pain | 2 (50) | 1 (25.0) | 0 | 1 (12.5) | 3 (25.0) |
| Arthralgia | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| Bone pain | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Muscle spasms | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| Musculoskeletal pain | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| **Nervous system disorders** | 2 (50) | 3 (75.0) | 2 (50) | 5 (62.5) | 7 (58.3) |
| Balance disorder | 0 | 1 (25.0) | 2 (50) | 3 (37.5) | 3 (25.0) |
| Headache | 2 (50) | 1 (25.0) | 0 | 1 (12.5) | 3 (25.0) |
| Dizziness | 1 (25.0) | 0 | 0 | 0 | 1 ( 8.3) |
| Somnolence | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |

## Table 12-2: Summary of Treatment-Emergent Adverse Events Through Week 24 (Safety Population)

| Body System/ Preferred Term | Placebo N = 4 n(%) | Eteplirsen 30 mg/kg/wk N = 4 n(%) | Eteplirsen 50 mg/kg/wk N = 4 n(%) | Eteplirsen All Eteplirsen N = 8 n(%) | All Patients[a] N = 12 n(%) |
|---|---|---|---|---|---|
| **General disorders & administration site conditions** | 2 (50) | 2 (50) | 2 (50) | 4 (50) | 6 (50) |
| Pyrexia | 2 (50) | 1 (25.0) | 0 | 1 (12.5) | 3 (25.0) |
| Injection site pain | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| Malaise | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| Non-cardiac chest pain | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Pain | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| **Metabolism & nutrition disorders** | 2 (50) | 2 (50) | 2 (50) | 4 (50) | 6 (50) |
| Hypokalaemia | 2 (50) | 2 (50) | 2 (50) | 4 (50) | 6 (50) |
| **Gastrointestinal disorders** | 2 (50) | 1 (25.0) | 2 (50) | 3 (37.5) | 5 (41.7) |
| Vomiting | 0 | 1 (25.0) | 2 (50) | 3 (37.5) | 3 (25.0) |
| Abdominal pain | 2 (50) | 0 | 0 | 0 | 2 (16.7) |
| Diarrhoea | 1 (25.0) | 0 | 1 (25.0) | 1 (12.5) | 2 (16.7) |
| Nausea | 1 (25.0) | 0 | 1 (25.0) | 1 (12.5) | 2 (16.7) |
| **Infections & infestations** | 3 (75.0) | 0 | 1 (25.0) | 1 (12.5) | 4 (33.3) |
| Rhinitis | 1 (25.0) | 0 | 1 (25.0) | 1 (12.5) | 2 (16.7) |
| Enterobiasis | 1 (25.0) | 0 | 0 | 0 | 1 ( 8.3) |
| Nasopharyngitis | 1 (25.0) | 0 | 0 | 0 | 1 ( 8.3) |
| Soft tissue infection | 1 (25.0) | 0 | 0 | 0 | 1 ( 8.3) |
| **Vascular disorders** | 1 (25.0) | 1 (25.0) | 1 (25.0) | 2 (25.0) | 3 (25.0) |
| Haematoma | 1 (25.0) | 1 (25.0) | 1 (25.0) | 2 (25.0) | 3 (25.0) |
| **Renal & urinary disorders** | 1 (25.0) | 1 (25.0) | 0 | 1 (12.5) | 2 (16.7) |
| Polyuria | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Proteinuria | 1 (25.0) | 0 | 0 | 0 | 1 ( 8.3) |
| **Skin & subcutaneous tissue disorders** | 0 | 2 (50) | 0 | 2 (25.0) | 2 (16.7) |
| Dermatitis contact | 0 | 2 (50) | 0 | 2 (25.0) | 2 (16.7) |
| Petechiae | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Urticaria thermal | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| **Cardiac disorders** | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |
| Tachycardia | 0 | 1 (25.0) | 0 | 1 (12.5) | 1 ( 8.3) |

## Table 12-2: Summary of Treatment-Emergent Adverse Events Through Week 24 (Safety Population)

| Body System/ Preferred Term | Placebo N = 4 n(%) | Eteplirsen 30 mg/kg/wk N = 4 n(%) | Eteplirsen 50 mg/kg/wk N = 4 n(%) | Eteplirsen All Eteplirsen N = 8 n(%) | All Patients[a] N = 12 n(%) |
|---|---|---|---|---|---|
| **Overall** | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |
| Motion sickness | 0 | 0 | 1 (25.0) | 1 (12.5) | 1 ( 8.3) |

Source: [redacted]

[a] Patients were counted once in each body system and preferred term.

### *12.2.3 Adverse Events by Severity*

Two patients in the 30 mg/kg/wk eteplirsen group experienced a total of 3 severe TEAEs during the study. Patient 006 experienced nasal congestion and Patient 009 experienced bone pain and transient loss of balance. None of these TEAEs were assessed as related to study medication or as serious. All other TEAEs in all treatment groups were assessed as mild or moderate. A tabular summary of TEAEs by severity is provided in [redacted] There were no severe TEAEs reported during the last 4 weeks of this study when all patients were receiving 30 or 50 mg/kg/wk eteplirsen [redacted]

### *12.2.4 Adverse Events by Relationship to Study Treatment*

One patient in the placebo group, Patient 008, experienced a TEAE of intermittent nausea (mild) that was assessed as possibly/probably related to study medication by the Investigator; all other TEAEs were considered unrelated to study medication. A tabular summary of TEAEs by relationship to study medication is provided in [redacted]. There were no treatment-related TEAEs reported during the last 4 weeks of this study when all patients were receiving 30 or 50 mg/kg/wk eteplirsen [redacted].

### *12.2.5 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events*

#### *12.2.5.1 Deaths*

There were no deaths during this study.

#### *12.2.5.2 Other Serious Adverse Events*

There were no SAEs during this study.

#### *12.2.5.3 Other Significant Adverse Events*

There were no other significant AEs during this study.

#### *12.2.5.4 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events*

No narratives are provided as there were no deaths, discontinuations due to AEs, SAEs or other significant AEs during this study.

## 12.3 Clinical Laboratory Evaluations

### *12.3.1 Chemistry*

Mean changes from baseline in the chemistry parameters assessed, including electrolytes, liver function tests, and renal function tests, were generally small and no clinically relevant changes from baseline were observed in any of the treatment groups.

Transient shifts at week 24 from baseline to low or high relative to the normal range for potassium, glucose, BUN, alkaline phosphatase, and GGT levels occurred sporadically across the treatment groups; however, no trends related to treatment (placebo vs. eteplirsen) or dose level of eteplirsen (30 vs. 50 mg/kg/wk) were observed. Moreover, there were no shifts to low or high in serum cystatin C or in any of the other chemistry parameters assessed and no abnormal chemistry result was assessed as clinically significant. As expected based on the population under study, all patients had elevated ALT, AST, creatine kinase (CK), and lactate dehydrogenase (LDH) levels at baseline and as a worst assessment on study.

[redacted] summarizes chemistry parameter values at baseline and over time by treatment group, [redacted] summarizes shifts (low, normal, high) at week 24 from baseline by parameter and group, and [redacted] summarizes treatment emergent markedly abnormal chemistry results by parameter, time point, and group. The by-patient listing of all chemistry results is provided in [redacted].

### *12.3.2 Coagulation*

Mean changes from baseline in the coagulation parameters assessed, including PT, aPTT, and INR, were generally small and no clinically relevant changes from baseline were observed for any of the treatment groups. No shifts at week 24 from baseline to low or high relative to the normal range were observed on any coagulation parameter in any treatment group, nor were any abnormal coagulation results assessed as clinically significant.

[redacted] summarizes coagulation parameter values at baseline and over time by treatment group and [redacted] summarizes shifts (low, normal, high) at week 24 from baseline by parameter and group. The by-patient listing of all chemistry results is provided in [redacted]

### *12.3.3 Hematology*

Mean changes from baseline in hematology parameters, including hemoglobin, hematocrit, RBC, WBC, platelets, basophils, eosinophils, monocytes, neutrophils, lymphocytes, and abnormal cells, were generally small and no clinically relevant changes from baseline were observed in any of the treatment groups. Shifts at week 24 from baseline to low or high relative to the normal range for hematology parameters occurred rarely and no trends related to treatment or dose level of eteplirsen were observed. Furthermore, no abnormal hematology results were assessed as clinically significant.

[redacted] summarizes hematology parameter values at baseline and over time by treatment group, [redacted] summarizes shifts (low, normal, high) at week 24 from baseline by parameter and group, and [redacted] summarizes treatment emergent markedly abnormal hematology results by parameter, time point, and group. The by-patient listing of all hematology results is provided in [redacted].

### *12.3.4 Urinalysis*

Mean changes from baseline in urine specific gravity, pH, cystatin C, and KIM-1, were generally small and no clinically relevant changes were observed in any of the treatment groups. There

were no shifts at week 24 from baseline from normal to low or high relative to the normal range in specific gravity, pH, or cystatin C; however, 1 patient in the placebo group experienced a shift from normal to low in KIM-1.

There were no shifts at week 24 from baseline from normal to abnormal in urine protein, glucose, ketones, bacteria, hemoglobin, WBC, casts, or crystals; however, 2 patients in the 50 mg/kg/wk eteplirsen group experienced a shift in RBC from normal to abnormal. No abnormal urinalysis results were assessed as clinically significant. One placebo-treated patient (008) experienced transient, mild proteinuria during week 8 which was not considered treatment-related, but was considered an AE.

[redacted] summarizes levels of the quantitative urinary parameters (specific gravity, pH, cystatin C, and KIM-1) at baseline and over time by treatment group, [redacted] summarizes shifts (low, normal, high) at week 24 from baseline by group for each of the quantitative parameters, and [redacted] summarizes treatment emergent markedly abnormal urinalysis results by time point and group for each of the quantitative parameters. All of the qualitative urinary parameters (protein, glucose, ketones, bacteria, WBC, RBC, casts, crystals, and hemoglobin) are summarized in [redacted] and shifts at week 24 from baseline from normal to abnormal for these parameters are summarized in [redacted] The by-patient listing of all urinalysis results is provided in [redacted]

### *12.3.5 ELISPOT Analysis*

[redacted] summarizes immune responses to novel dystrophin protein at baseline through week 24 by treatment group. The by-patient listing of all ELISPOT results is provided in [redacted]. There were no clear differences between the placebo- and eteplirsen-treated patients in the number of interferon-γ induced spot forming colonies to dystrophin peptide pools (which extended over the entire protein) at any time point, including week 24, indicating that the newly expressed dystrophin in the eteplirsen-treated patients did not elicit a T-cell response.

### *12.3.6 Clinically Significant Laboratory Findings*

There were no clinically significant laboratory abnormalities during the conduct of this study.

## 12.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

### *12.4.1 Vital Signs*

Vital signs, including weight, heart rate and blood pressure were taken at every visit from screening through week 28/early termination. No trends related to treatment or dose level of eteplirsen were observed for any of the vital signs parameters assessed and no changes in vital signs parameters were assessed as clinically significant.

[redacted] summarizes heart rate and blood pressure over time and by treatment group, while [redacted] summarizes markedly abnormal heart rate and blood pressure results by time point and group. The by-patient listing of all blood pressure and heart rate findings is provided in [redacted] and height and weight results are listed by patient in [redacted]

### 12.4.2 Physical Examination Findings

All patients experienced clinically significant physical examination findings, the majority of which were related to certain study procedures such as the muscle biopsies (e.g., abnormal healing of biopsy wound site) or were expected based on their DMD diagnosis (e.g., heel cord contractures). Physical examination findings are provided for each patient in [redacted].

### 12.4.3 Electrocardiogram Findings

A 12-lead ECG was performed at screening/baseline and [redacted] following study drug administration at weeks 12 and 24. Mean changes from baseline in ECG findings including heart rate (HR) and PR, QRS, QT, QTcB (QT interval corrected with Bazett's formula), and QTcF (QT interval corrected with Fridericia's formula) were generally small and no clinically relevant changes were observed in any of the treatment groups.

[redacted]

[redacted] summarizes ECG findings at baseline and over time by treatment group, [redacted] summarizes treatment emergent markedly abnormal ECG findings by parameter, time point, and group, and [redacted] summarizes shifts at week 24 from baseline in ECG parameters. The by patient listing of all ECG results is provided in [redacted].

### 12.4.4 Echocardiograms

Echocardiograms were performed [redacted]. No trends related to time, treatment, or dose level were observed in EF or FS, and no ECHO findings were assessed as clinically significant.

[redacted] summarizes ECHO findings at baseline and over time by treatment group and the by-patient listing of all ECHO results is provided in [redacted]

### 12.4.5 Pregnancies

As expected given the gender and age of the study participants, there were no pregnancies during the conduct of this study.

### 12.4.6 Summary of Safety Findings

- IV infusions of 30 or 50 mg/kg/wk eteplirsen for 28 weeks were well tolerated.
- A total of 99 TEAEs were reported, most of which were related to the required muscle biopsies or were consistent with signs and symptoms typically seen in pediatric patients and those with DMD. The most commonly reported TEAEs included procedural pain,

oropharyngeal pain, [redacted] cough, nasal congestion, and extremity pain. No relationship between the occurrence of specific TEAEs and treatment (placebo vs. eteplirsen) or dose of eteplirsen (50 vs. 30 mg/kg/wk) was observed.

- All TEAEs but 1 (nausea in a placebo patient) were assessed as unrelated to study medication, and all but 3 (nasal congestion, bone pain and transient loss of balance in 2 30 mg/kg/wk eteplirsen patients) were assessed as mild or moderate in intensity.

- There were no SAEs, discontinuations due to AEs, or deaths.

- Change from baseline in safety laboratory tests (chemistry, coagulation, hematology, and urinalysis), measures of renal function (serum cystatin C and urine cystatin C and KIM-1), and vital signs were generally small and no trends related to treatment (placebo vs. eteplirsen) or dose level of eteplirsen (30 vs. 50 mg/kg/wk) were observed. In addition, no abnormal safety laboratory findings (including measures of renal function) or changes from baseline in vital signs were assessed as clinically significant. One placebo-treated patient experienced transient and mild proteinuria [redacted] that was considered an AE.

- With respect to cardiac function, changes from baseline in ECG and ECHO findings were generally small and none were assessed as clinically significant.
- There were no clear differences between the placebo- and eteplirsen-treated patients in the number of interferon-γ induced spot forming colonies to dystrophin peptide indicating that the newly expressed dystrophin in the eteplirsen-treated patients did not elicit a T cell response.

# 13 DISCUSSION AND OVERALL STUDY CONCLUSIONS

In DMD, deletions, mutations, or duplications in specific exons of the dystrophin gene disrupt the open-reading frame, essentially precluding the synthesis of dystrophin, a protein critical to the structural stability of myofibers in skeletal and cardiac muscle. In the absence of dystrophin, affected boys usually develop muscle weakness in the first few years of life, lose the ability to walk during childhood, require respiratory support by their late teens, and succumb to cardiac or pulmonary failure in their 20s (Brooke 1989, Eagle 2002, Kohler 2009).

Sarepta is developing several exon-specific, splice-switching PMOs to directly address the underlying cause of DMD. Sarepta's lead DMD therapy, eteplirsen, is designed to selectively bind to exon 51 of the dystrophin pre-mRNA. This causes the exon to be skipped during processing and restores the open-reading frame and the synthesis of dystrophin protein in patients with deletions amenable to correction by exon 51 skipping. This includes patients with deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63, representing approximately 13% of all DMD patients (Aartsma-Rus 2009). Eteplirsen's ability to induce exon 51 skipping and produce functional dystrophin that contains a relatively small internal deletion in patients with DMD has already been confirmed in 2 prior open-label clinical studies: AVI-4658-33, which examined the effect of a single IM dose of eteplirsen, and AVI-4658-28, which examined the effect of 12 intravenous infusions of eteplirsen at doses ranging from 0.5 to 20 mg/kg/wk.

The present study, 4658-us-201, is the first randomized, double-blind, placebo-controlled study of eteplirsen in patients with DMD. A total of 12 boys received one of the following treatments: 50 mg/kg/wk eteplirsen for 28 weeks (n = 4); 30 mg/kg/wk eteplirsen for 28 weeks (n = 4); or placebo for 24 weeks followed by 4 weeks of 50 mg/kg/wk eteplirsen (n = 2) or 30 mg/kg/wk eteplirsen (n = 2). All patients underwent muscle biopsies at baseline for analysis of exon skipping and dystrophin expression. Repeat biopsies were performed at Week 12 for the 50 mg/kg/wk eteplirsen patients and 2 placebo patients and at Week 24 for the 30 mg/kg/wk eteplirsen patients and the other 2 placebo patients. Efficacy was assessed through the first 24 placebo-controlled weeks of this study, while safety was assessed through Week 28. Upon completion of this study, all 12 patients were enrolled into an open-label extension study (4658-us-202) to continue receiving once-weekly treatment with eteplirsen.

As expected, all 8 of the patients who began receiving eteplirsen at Week 1 showed post-treatment evidence of exon-skipping regardless of dose (50 mg/kg/wk vs. 30 mg/kg/wk) or duration (12 vs. 24 weeks). More importantly, once-weekly treatment with 30 mg/kg eteplirsen for 24 weeks significantly increased the percentage of dystrophin-positive muscle fibers in DMD patients compared to placebo ($p \leq 0.002$), thus, the pre-specified, primary efficacy endpoint for this study was met. Patients treated with 30 mg/kg/wk eteplirsen demonstrated a mean increase from baseline in the percentage of dystrophin-positive fibers to 41.4% of normal at Week 24. In contrast, there were no detectable mean increases from baseline in the percentage of dystrophin-positive fibers in placebo-treated patients biopsied at Weeks 12 or 24. There were also no detectable mean increases from baseline in the 50 mg/kg/wk eteplirsen-treated patients biopsied at Week 12, suggesting that eteplirsen-induced increases in the percentage of dystrophin-positive fibers are dependent on duration of treatment. Consistent with these results, only those patients who received 30 mg/kg/wk eteplirsen for 24 weeks demonstrated an increase

from baseline in dystrophin protein levels as measured by Western blot. Increases from baseline in the intensity of dystrophin-positive fibers (as measured by IHC) were detectable after 12 weeks of treatment with 50 mg/kg/wk eteplirsen and after 24 weeks of treatment with 30 mg/kg/wk eteplirsen.

The absence of a detectable increase in the percentage of dystrophin-positive fibers after 12 weeks of treatment with 50 mg/kg/wk eteplirsen (even though all 4 patients demonstrated exon skipping as well as an increase in dystrophin intensity per fiber at that time point) is likely due to a combination of factors. [redacted] Furthermore, it has been suggested that because splice switching oligomers do not target skeletal muscle specifically, their uptake is partly dependent on local events such as muscle perfusion, damage, and inflammation. Dystrophic muscle undergoes accelerated cycles of degeneration and regeneration, with some cells having less stable (more permeable or leaky) membranes than others at any point in time. It is possible that these cells take up more drug, allowing them to respond more robustly than other cells. With repeated doses over time, many more cells may be accessed by the drug, leading to a larger number of dystrophin-positive muscle fibers.

With respect to eteplirsen's clinical efficacy, performance on measures involving ambulation, including the 6MWT, Timed 4-Step Test, and several components of the NSAA, was highly variable across patients with some showing minor improvements from baseline, most remaining stable, and 2 patients in the 30 mg/kg/wk eteplirsen showing rapid (within 8 weeks of first dose) and marked decline. This variability, combined with the small sample size, made it difficult to detect clear between-group differences. It is also possible, for the reasons discussed above, that longer periods of treatment will be required to detect an effect of eteplirsen on functional ability. Performance on measures of upper body muscle strength and function including the MVICT, the 9-Hole Peg Test, and PFT was stable across the 24-week assessment period regardless of treatment or dose, which was not unexpected given the age and the stage of disease progression of the patients in this study. Changes in upper arm strength and respiratory function are typically not observed in DMD until the mid to late teen years.

Overall, eteplirsen was well tolerated. Adverse events were largely consistent with the procedures performed in this study (i.e., muscle biopsies) and/or the types of events typically seen in pediatric patients with DMD. Moreover, there was no relationship between the occurrence of specific TEAEs and treatment (placebo vs. eteplirsen) or dose of eteplirsen (50 vs. 30 mg/kg/wk). The most commonly reported TEAEs included procedural pain, oropharyngeal pain, [redacted], cough, nasal congestion, and extremity pain. All TEAEs but 1 (nausea in a placebo patient) were assessed as unrelated to study medication, and all but 3 (nasal congestion, bone pain and transient loss of balance in two 30 mg/kg/wk eteplirsen patients) were assessed as mild or moderate in intensity. There were no SAEs, discontinuations due to AEs, or deaths. Laboratory assessments, including measures of renal function, were generally stable throughout the study and there were no trends related to treatment (placebo vs. eteplirsen) or dose level of eteplirsen (30 vs. 50 mg/kg/wk). In addition, no abnormal safety laboratory findings (including measures of renal function) or changes from baseline in vital signs were assessed as clinically significant. With respect to cardiac function, changes from baseline in ECG and ECHO findings were generally small and none were assessed as clinically significant.

Regardless of dose, plasma concentrations of eteplirsen at 5 minutes post-infusion were similar at Weeks 12 and 24. Between the 30 and 50 mg/kg/wk dose levels, $C_{max}$ increased in a dose-proportional manner, while AUC increased in a somewhat greater than proportional manner; $CL_{PL}$, $V_{ss}$ and half-life were similar across the 2 dose levels. Consistent with prior studies (AVI-4658-28), the half-life of eteplirsen was approximately 3 hours. Given this, and the rapid decline in concentrations observed over 24 hours ($AUC_{0-24}$ accounted for >95% of $AUC_{0-\infty}$), little if any accumulation would be expected upon repeated once-weekly dosing of eteplirsen. Mean renal clearance of unchanged eteplirsen accounted for approximately 64.1% and 69.5% of total systemic clearance, respectively.

## 13.1 Overall Conclusions

Once-weekly IV infusions of eteplirsen, at doses of 30 or 50 mg/kg for up to 28 weeks, were well-tolerated in this small sample of boys with DMD. Exon 51 skipping was demonstrated post-treatment in 100% of patients who received eteplirsen, and time-dependent increases in dystrophin expression were observed across the 3 assays used for evaluation. When balanced against the progressive and ultimately fatal nature of DMD, the current findings demonstrate that treatment with eteplirsen for 24 weeks induces production of dystrophin, the protein necessary for muscle function, in patients with DMD who are amenable to exon 51 skipping treatment. These promising results support the continued evaluation of eteplirsen to confirm that the observed induction of dystrophin protein production in treated patients will translate into measurable clinical benefit.

# 14 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

## 14.1 Demographic Data Summary Tables and Figures

| Table Number | Table Title |
|---|---|
| Table 14.1.1 | Summary of Subject Disposition (All Patients Enrolled) |
| Table 14.1.2 | Summary of Demographics and Other Baseline Characteristics (Safety Population) |
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## 14.2 Efficacy Data Summary Tables

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|---|---|
| Table 14.2.1.1.1 | Summary of Muscle Biopsy (Full Analysis Population) |
| Table 14.2.1.1.2 | Analysis of Change from Baseline for Muscle Biopsy (Full Analysis Population) |
| Table 14.2.1.2.1 | Summary of Lymphocyte Counts in Muscle Biopsy (Full Analysis Population) |
| [redacted] | [redacted] |
| Table 14.2.1.3 | Summary of Exon Skipping (Full Analysis Population) |
| Table 14.2.2.1 | Summary and Change from Baseline of North Star Ambulation Assessment (Full Analysis Population) |
| Table 14.2.2.2.1 | Analysis of Change from Baseline for North Star Ambulation Assessment (Full Analysis Population) |
| Table 14.2.2.2.2 | Analysis of Change from Baseline for North Star Ambulation Assessment using Ranked Data (Full Analysis Population) |
| Table 14.2.2.2.3 | Supporting Documentation for Analysis of Change from Baseline for North Star Ambulation Assessment (Full Analysis Population) |
| Table 14.2.2.3 | Analysis of Change from Baseline by Number (%) of Subject for the components of North Star Ambulation Assessment (Full Analysis Population) |

[redacted]

| Table Number | Table Title |
|---|---|
| [redacted] | |
| Table 14.2.5.1 | Summary and Change from Baseline of 6 Minute Walk Test (Full Analysis Population) |
| Table 14.2.5.2.1 | Analysis of Change from Baseline for 6 Minute Walk Test (Full Analysis Population) |
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| Table 14.2.5.6.2 | Analysis of Change from Baseline for 6 Minute Walk Test using Ranked Data of Minimum Value (Full Analysis Population) |
| Table 14.2.5.6.3 | Supporting Documentation for Analysis of Change from Baseline of 6 Minute Walk Test Using Minimum Value (Full Analysis Population) |
| Table 14.2.6.1 | Summary and Change from Baseline of Timed 4 Step Test (Full Analysis Population) |
| [redacted] | |

| Table Number | Table Title |
|---|---|
| Table .14.2.5.6.1 | Analysis of Change from Baseline for 6 Minute Walk Test Using Minimum Values (Full Analysis Population – Subjects 009 and 010 Excluded) |
| Table .14.2.5.6.2 | Analysis of Change from Baseline for 6 Minute Walk Test using Ranked Data of Minimum Value (Full Analysis Population – Subjects 009 and 010 Excluded) |
| Table .14.2.5.6.3 | Supporting Documentation for Analysis of Change from Baseline of 6 Minute Walk Test Using Minimum Values (Full Analysis Population – Subjects 009 and 010 Excluded) |
| [redacted] | |

## 14.3 Safety Data Summary Tables

### *14.3.1 Display of Adverse Events*

| Table Number | Table Title |
|---|---|
| Table 14.3.1.1 | Summary of Treatment Emergent Adverse Events (Safety Population) |
| Table 14.3.1.2 | Summary of Treatment Related Treatment Emergent Adverse Events (Safety Population) |
| Table 14.3.1.3 | Summary of Treatment Emergent Adverse Events by Severity (Safety Population) |
| Table 14.3.1.4 | Summary of Treatment Related Treatment Emergent Adverse Events by Severity (Safety Population) |
| Table 14.3.1.5 | Summary of Serious Adverse Events (Safety Population) |

### *14.3.2 Listings of Deaths, Serious Adverse Events, and Significant Adverse Events*

There were no deaths, other serious adverse events, or withdrawals for adverse events in this study.

### *14.3.3 Narratives of Deaths, Serious Adverse Events, and Significant Adverse Events*

There were no deaths, other serious adverse events, or withdrawals for adverse events in this study.

### 14.3.4 Laboratory Values

| Table Number | Table Title |
|---|---|
| Table 14.3.4.1.1 | Summary and Change from Baseline of Serum Chemistry Laboratory Parameters (Safety Population) |
| Table 14.3.4.1.2 | Shift Table of Serum Chemistry Laboratory Parameters (Safety Population) |
| Table 14.3.4.1.3 | Summary of Treatment Emergent Markedly Abnormal Results of Serum Chemistry Laboratory Parameters (Safety Population) |
| Table 14.3.4.2.1 | Summary and Change from Baseline of Coagulation Laboratory Parameters (Safety Population) |
| Table 14.3.4.2.2 | Shift Table of Coagulation Laboratory Parameters (Safety Population) |
| Table 14.3.4.3.1 | Summary and Change from Baseline of Hematology Laboratory Parameters (Safety Population) |
| Table 14.3.4.3.2 | Shift Table of Hematology Laboratory Parameters (Safety Population) |
| Table 14.3.4.3.3 | Summary of Treatment Emergent Markedly Abnormal Results of Hematology Laboratory Parameters (Safety Population) |
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| Table 14.3.4.5 | Summary of T Cell Response to Dystrophin (ELI Spot Analysis) (Safety Population) |
| Table 14.3.5.1 | Summary of Vital Signs (Safety Population) |
| Table 14.3.5.2 | Summary of Treatment Emergent Markedly Abnormal Results of Vital Signs (Safety Population) |
| Table 14.3.6.1 | Summary of 12-lead ECG Results (Safety Population) |
| Table 14.3.6.2 | Summary of Treatment Emergent Markedly Abnormal Results of 12-lead ECG (Safety Population) |
| Table 14.3.6.3 | Shift Table of 12-lead ECGs (Safety Population) |
| Table 14.3.7 | Summary of Echocardiography Results (Safety Population) |
| Table 14.3.8 | Summary of Concomitant Medication (Safety Population) |

# 15 REFERENCE LIST

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# 16 APPENDICES

## 16.1 Study Information

| | |
|---|---|
| 16.1.1 | Protocol and Protocol Amendments |
| 16.1.2 | Sample Case Report Form |
| 16.1.3.1 | List of IECs and/or IRBs |
| 16.1.3.2 | Representative Written Information for Patient and Sample Informed Consent Forms |
| 16.1.4 | List and Description of Investigators and Other Important Participants in the Study, including CVs |
| 16.1.5 | Signature of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer |
| 16.1.6 | Listing of Patients Receiving Investigational Product from Specific Batches Where More than One Batch was Used |
| 16.1.7 | Randomization Scheme and Codes |
| 16.1.8 | Audit Certificates |
| 16.1.9 | Documentation of Statistical Methods |
| 16.1.10 | Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures |
| 16.1.11 | Publications Based on the Study |
| 16.1.12 | Important Publications Referenced in the Report |

## 16.2 Patient Data Listings

### *16.2.1 Discontinued Patients*

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.1.1* | *Randomization Assignments (All Patients Enrolled)* |
| Listing *16.2.1.2* | *Subject Disposition (All Subjects Enrolled)* |

### *16.2.2 Protocol Deviations*

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.2* | *Protocol Deviations (Safety Population)* |

### *16.2.3 Patients Excluded from the Efficacy Analysis*

No patient was excluded from efficacy analyses for the full analysis population (FAS).

However, 2 patients (009 and 010) were exlcuded in a modified intent-to-treat (mITT) analysis of the functional efficacy endpoint (e.g., 6-minute walk test). These 2 patients were twins with the lowest distance walked at Baseline, and they were among the oldest boys enrolled. Both boys lost ambulation early in the study (<24 weeks), resulting in data that deviated significantly from normal; thus, the boys were considered to be outliers. Data for the patients included in the mITT population were normally distributed.

### *16.2.4 Demographic Data*

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.4.1* | *Demographics and Other Baseline Characteristics (Safety Population)* |
| Listing *16.2.4.2* | *Medical History (Safety Population)* |

### *16.2.5 Compliance and/or Drug Concentration Data*

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.5.1* | *Drug Administration (Safety Population)* |
| Listing *16.2.5.2* | *Prior and Concomitant Medications (Safety Population)* |
| Listing *16.2.5.3.1* | *Plasma Pharmacokinetic Sampling (Safety Population)* |
| Listing *16.2.5.3.2* | *Urine Pharmacokinetic Sampling (Safety Population)* |

### 16.2.6 Individual Efficacy Response Data

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.6.1.1* | *Dystrophin Positive Fibers on IHC (All Patients Enrolled)* |
| Listing *16.2.6.1.2.1* | *Dystrophin Expression per Fiber Measured by Bioquant (All Patients Enrolled)* |
| Listing *16.2.6.1.2.2* | *Dystrophin Expression per Fiber Measured by Bioquant – Re-Analysis (All Patients Enrolled)* |
| Listing *16.2.6.1.3.1* | *Total Dystrophin Protein by Western Blot Analysis (All Patients Enrolled)* |
| Listing *16.2.6.1.3.2* | *Total Dystrophin Protein by Western Blot Analysis – Re-Analysis (All Patients Enrolled)* |
| [redacted] | |
| Listing *16.2.6.1.6.1* | *Exon Skipping (Assessed by RT-PCR) in Muscle Biopsy Tissue (All Patients Enrolled)* |
| Listing *16.2.6.1.6.2* | *Exon Skipping (Assessed by RT-PCR) in Muscle Biopsy Tissue – Re-Analysis (All Patients Enrolled)* |
| Listing *16.2.6.2* | *North Star Ambulation Assessment (Full Analysis Population)* |
| [redacted] | |
| Listing *16.2.6.5* | *6 Minute Walk Test (Full Analysis Population)* |

| Listing Number | Listing Title |
|---|---|
| [redacted] | |
| Listing *16.2.6.8* | *Pulmonary Function Tests (Full Analysis Population)* |

### *16.2.7 Adverse Event Listings (each patient)*

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.7* | *Adverse Events (Safety Population)* |

### *16.2.8 Listing of Individual Laboratory Measurements (by patient)*

| Listing Number | Listing Title |
|---|---|
| Listing *16.2.8.1.1* | *Chemistry Laboratory Results (Safety Population)* |
| Listing *16.2.8.1.2* | *Coagulation Laboratory Results (Safety Population)* |
| Listing *16.2.8.1.3* | *Hematology Laboratory Results (Safety Population)* |
| Listing *16.2.8.1.4* | *Urinalysis Laboratory Results (Safety Population)* |
| Listing *16.2.8.1.5* | *T Cell Response to Dystrophin (Eli Spot Analysis) (Safety Population)* |
| Listing *16.2.8.2.1* | *Vital Signs (Safety Population)* |
| Listing *16.2.8.2.2* | *Height and Weight (Safety Population)* |
| Listing *16.2.8.3* | *12-lead ECG Results (Safety Population)* |
| Listing *16.2.8.4* | *Echocardiography Test Results (Safety Population)* |
| Listing *16.2.8.5* | *Holter Monitoring Results at Screening (Safety Population)* |
| Listing *16.2.8.6* | *Physical Examination (Safety Population)* |

## 16.3 Case Report Forms

There were no deaths, other serious adverse events, or withdrawals for adverse events in this study.

## 16.4 Individual Patient Data Listings

Not applicable.

## 16.5 Pharmacokinetic Report

Refer to Appendix 16.5 for the Pharmacokinetic Report (17 September 2012).

# ERRATA FOR THE CLINICAL STUDY REPORT 4658-us-201

## REASON FOR ERRATA

The clinical study report (CSR) for the trial entitled *"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"* was finalized and signed on 19 November 2014 by Jerry R. Mendell, MD (Principal Investigator, Nationwide Children's Hospital and the Ohio State University) and by Edward M. Kaye, MD, Interim Chief Executive Officer, Chief Medical Officer, and Senior Vice President, Clinical Development at Sarepta Therapeutics, Inc. (Appendix 16.1.5).

After the finalization of the CSR, the following data issues were identified via internal review and are presented in Table 1 below. None of these findings were considered major and none affect the integrity of the CSR or conclusions therein.

**Table 1: Table of Discrepancies**

| Subject | Visit | Assay | Antibody | Block | Level | Issue | Errata | Explanation / Consequence |
|---|---|---|---|---|---|---|---|---|
| 01003 | Week 12 | PDPF[a] | DYS2 | B | L3 | Image 3 and 4 are of same biopsy tissue section field | A 5th field was captured and used for analysis | Images 3 and 4 were determined to be the same field - therefore, a 5th field was photographed and quantified. Minimal to no impact for CSR. |
| 01010 | Baseline and Week 24 | 40x BQ[b] | - | N/A | N/A | Images 1 and 3 are of same field | No corrective action taken | Should be 4 images, one per quadrant, of each section of the tissue. However, image 3 is a duplicate of image 1. Minimal to no impact for CSR. |
| 01010 | Baseline and Week 24 | 40x BQ[b] | - | N/A | N/A | Images 2 and 4 are of same field | No corrective action taken | Should be 4 images, one per quadrant, of each section of the tissue. However, image 4 is duplicate of image 2. Minimal to no impact for CSR. |
| 01010 | Baseline and Week 24 | WB[c] | MANDYS106 | N/A | N/A | No labels on gel | No corrective action taken | There are no labels for this gel on the gel nor in slide deck. Cannot confirm which lanes are Baseline and Week 24. Minimal to no impact for CSR. |

[a] Percentage of dystrophin-positive fibers
[b] Bioquant
[c] Western blot