

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

**PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE**

25 April 2016

**ETEPLIRSEN BRIEFING DOCUMENT
NDA 206488**



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LIST OF ABBREVIATIONS

| Abbreviation/Term | Definition |
|-------------------|---|
| 6MWT | 6-Minute Walk Test |
| 6MWD | 6-Minute Walk Distance |
| AA | Accelerated Approval |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| ATS | American Thoracic Society |
| AUC | area under the concentration time curve |
| AVI-4658 | eteplirsen |
| BL | Baseline |
| BLOQ | below the limit of quantification |
| BMD | Becker muscular dystrophy |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CDC | Centers for Disease Control |
| CK | creatinine kinase |
| CLPL | plasma clearance |
| C _{max} | maximum concentration |
| CYP | cytochrome P450 enzymes |
| CXMD | canine X-linked muscular dystrophy |
| DAPC | dystrophin-associated protein complex |
| DMD | Duchenne muscular dystrophy |
| <i>DMD</i> gene | dystrophin gene |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| EDB | extensor digitorum brevis |
| EF | ejection fraction |

| | |
|---------|---|
| EK | Egen Klassifikation |
| ELISPOT | enzyme-linked immunosorbent spot assay |
| FDA | Food and Drug Administration |
| FVC | forced vital capacity |
| GGT | gamma-glutamyltransferase |
| GLP | Good Laboratory Practices |
| hDMD | humanized DMD mouse model |
| HR | heart rate |
| ICC | interclass correlation coefficient |
| ICH | International Conference on Harmonisation |
| IHC | immunohistochemistry |
| IM | intramuscular, intramuscularly |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| IV | intravenous, intravenously |
| LOCF | last observation carried forward |
| LVEF | left ventricular ejection fraction |
| Max | maximum |
| mdx | dystrophic mouse model |
| MEP | maximum expiratory pressure |
| Min | minimum |
| MIP | maximum inspiratory pressure |
| MMRM | mixed model repeated measure |
| MVICT | maximum voluntary isometric contraction testing |
| NA | not applicable |
| NDA | New Drug Application |
| NHP | non-human primates |
| NMRC | Neuromuscular Reference Center |
| N/n | number |
| nNOS | nitric oxide synthase |
| NOAEL | no observed adverse effect level |
| NSAA | North Star Ambulatory Assessment |
| PDPF | Percentage of dystrophic positive fibers |

| | |
|------------------|---|
| PFTs | pulmonary function tests |
| PK | pharmacokinetic |
| PMO | Phosphorodiamidate morpholino oligomer |
| PODCI | Pediatric Outcomes Data Collection Instrument |
| PPMD | Parent Project Muscular Dystrophy |
| PT | prothrombin time |
| PUL | Performance Upper Limb Scale |
| QMT | quantitative muscle testing |
| RT-PCR | reverse transcription polymerase chain reaction |
| SAE | serious adverse event |
| SAM | step activity monitor |
| SD | standard deviation |
| SOC | System Organ Class |
| t _{1/2} | elimination half life |
| TA | tibialis anterior |
| TEAE | treatment emergent adverse event |
| ULN | upper limit of normal |
| United Kingdom | UK |
| US | United States |
| V _{ss} | apparent volume of distribution at steady-state |
| WB | Western blot |

1. EXECUTIVE SUMMARY

Introduction

Sarepta Therapeutics, Inc. (Sarepta) and the FDA have no more critical challenge than to reliably bridge and extend the benefits of medical innovation to patients. Eteplirsen has been developed as an innovative therapy, customized to treat a specific subset of DMD genetic mutations, those which are amenable to skipping exon 51.

Sarepta is seeking accelerated approval (AA) for eteplirsen administered as weekly 30 mg/kg IV infusions for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. This executive summary provides an overview of the attributes of the eteplirsen development program that specifically meet the criteria listed below as requirements for accelerated approval. A complete description of the clinical and nonclinical results of the development program for eteplirsen is provided in respective sections of this briefing document that follow this executive summary.

Key Changes to Previous Briefing Document

This version of Sarepta's PCNS Drug Advisory Committee briefing document contains new and updated information to that provided in the original Sarepta briefing document and addendum (dated 22 January 2016) previously posted on 15 January 2016, including:

- Supportive care and physiotherapeutic intervention data for eteplirsen-treated patients enrolled in Study 201/202
- Supportive care, physiotherapeutic intervention, physical exam data for the primary external control group (n=13)
- Week 216 functional endpoint data for eteplirsen-treated patients enrolled in Study 201/202
- Year 4 6MWT data for the primary external control group

In addition, this document provides clarification to information contained in the original FDA PCNS Drug Advisory Committee briefing document (dated 22 January 2016) previously posted on 15 January 2016 in [Appendix 19](#).

Regulatory Framework

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) codified FDA's accelerated approval authority. The statute provides that FDA may grant AA of a product:

“for a serious or life-threatening disease or condition” that “has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.”

This uncertainty about whether the ultimate clinical benefit will be achieved is accounted for by the requirement that a product approved under the accelerated approval program have:

“appropriate post-approval studies to verify and describe the predicted effect,” which are generally referred to as confirmatory postmarketing studies. FD&C Act §506(c)(2)(A). FDA’s regulations explain that at the time of accelerated approval, the “[p]ostmarketing studies would usually be studies already underway.” 21 C.F.R. §314.510.

The accelerated approval pathway means that there will be an acceptable degree of uncertainty about whether the therapy will actually result in the anticipated clinical benefit. This uncertainty is addressed by the requirement that “appropriate post-approval studies to verify and describe the predicted effect” would usually be underway at the time of approval.

Examples of FDA’s Flexibility

Historically, FDA has exercised some form of regulatory flexibility in the approval of new drugs for serious and rare conditions with unmet medical needs (Sasinowski 2015). Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs. “Adequate and well-controlled studies” must have “*a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.*” 21 C.F.R. §314.126(b)(2). FDA recognizes historically controlled studies, where “[t]he results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition...,” to be “adequate and well-controlled.” 21 C.F.R. §314.126(b)(2)(v). Specifically related to the development of drugs for DMD, FDA has acknowledged that in some circumstances, trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval (FDA Draft Guidance: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment, June 2015).

In prior drug approvals, FDA has determined that studies with small numbers of patients, as well as comparison to untreated historical controls, were adequately and well-controlled and thus met the “substantial evidence” standard of effectiveness. An example of FDA’s flexibility is demonstrated in the approval of Myozyme (alglucosidase alfa) for the treatment of patients with infantile onset Pompe disease. The approval precedent reflects the use of a natural history database to create a subgroup-matched historical control, selecting patients from the broader population that meet certain prognostic factors (e.g., age, age of onset, documented phenotype).

Brief Summary of the Regulatory History of Eteplirsen

The regulatory history of eteplirsen is non-traditional, in that the principal basis for establishing the effectiveness of eteplirsen is a comparison of patients in Study 201/202 to a historical control group of untreated DMD subjects (subsequently referred to as the external control group). During 2013-2015, Sarepta had extensive discussions and interactions with the FDA. As a result,

FDA provided Sarepta with a defined pathway for a fileable eteplirsen NDA. This included a clearly defined data package, as well as agreement to conducting two post approval confirmatory studies.

Following the submission of additional 4-year longitudinal data for external control subjects, FDA extended the review goal date by 3 months in order to provide time for a full review of the submission. The extended user fee goal date is May 26, 2016.

Additional detail is provided in [Section 3.4](#) and [Appendix 1](#).

Eteplirsen Is Intended to Treat a Rare Serious Medical Condition

Duchenne Muscular Dystrophy (DMD) is a serious, progressively debilitating, and ultimately fatal inherited X-linked neuromuscular disease. DMD is caused by mutations in the dystrophin gene that disrupt the mRNA reading frame, resulting in a lack of dystrophin, a critically important part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, patients with DMD follow a predictable disease course. Affected boys develop muscle weakness in the first few years of life, lose the ability to walk during childhood, and usually require respiratory support by their late teens. Loss of functional abilities leads to loss of independence and increasing caregiver burden. Once lost, these abilities cannot be recovered. Despite improvements in the standard of care, such as the use of glucocorticoids, DMD remains an ultimately fatal disease, with patients usually dying of respiratory or cardiac failure in their mid to late 20s.

The prevalence of DMD in the US is approximately 9,000 to 12,000. Approximately 13% of DMD patients have mutations of the dystrophin gene that are amenable to therapies that skip exon 51, which corresponds to ~1,300-1,900 patients in the US.

High Unmet Medical Need in DMD

There are no approved therapies for DMD in the US. The current standard of care guidelines for the treatment of DMD include the administration of glucocorticoids in conjunction with palliative interventions. While glucocorticoids may delay the loss of ambulation, they do not sufficiently ameliorate symptoms, modify the underlying genetic defect or address the absence of functional dystrophin characteristic of DMD.

Eteplirsen is a Targeted Therapy Specifically Designed to Treat DMD Patients Amenable to Exon 51 Skipping

Progressive loss of muscle tissue and function in DMD is caused by the absence or near absence of functional dystrophin; a protein that plays a vital role in the structure and function of muscle cells. A potential therapeutic approach to the treatment of DMD is suggested by Becker muscular dystrophy (BMD), a milder dystrophinopathy. Both dystrophinopathies are caused by mutations in the *DMD* gene. In DMD, mutations that disrupt the pre-mRNA reading frame, referred to as “out-of-frame” mutations, prevent the production of functional dystrophin. In BMD, “in-frame” mutations do not disrupt the reading frame and result in the production of internally shortened, functional dystrophin protein.

Eteplirsen was designed to target dystrophin pre-mRNA to induce skipping of exon 51, so that exon 51 is excluded or skipped from the mature, spliced mRNA transcript. By skipping exon 51, the disrupted reading frame is restored, enabling production of internally shortened dystrophin protein, analogous to BMD. While DMD encompasses various genetic subtypes, eteplirsen was specifically designed to skip exon 51 which comprises 13% of DMD mutations.

Eteplirsen is a Phosphorodiamidate Morpholino Oligomer

Eteplirsen is a phosphorodiamidate morpholino oligomer, or PMO, which represents a new and unique chemistry, structurally and biologically distinct from other synthetic antisense RNA therapeutics, such as phosphorothioates. The key difference lies in the oligomer backbone chemistry, which was designed to resist enzymatic degradation and provide stability *in vitro*. In contrast to other RNA therapeutics for DMD, there have been no observations of immunogenicity, vasculitis, thrombocytopenia or coagulopathy in nonclinical or clinical studies of PMOs.

Pivotal Study 201/202

Study 201 is a completed randomized, double-blind, placebo-controlled study of eteplirsen in 12 boys with DMD mutations amenable to exon 51 skipping who were in the ambulatory decline phase of disease (age ≥ 7 years and baseline 6MWT 180-440 meters). Eligible patients were randomized to receive weekly IV infusions of 30 mg/kg (N = 4), 50 mg/kg eteplirsen (N = 4) or placebo (N = 4) for the first 24 weeks.

- Following completion of the 24-week placebo-controlled period, the 4 placebo patients rolled over to open-label eteplirsen at a dose of either 30 mg/kg (N = 2) or 50 mg/kg (N = 2). Combined with the 8 patients randomized to eteplirsen, this pooled group of 12 patients has continued receiving eteplirsen in the ongoing extension Study 202.
- The primary endpoint of Study 201 was percent dystrophin positive fibers (PDPF). Significant dystrophin production was observed at the 24 week time-point for the 30 mg/kg dose group. Significant dystrophin was not observed at the earlier 12 week time-point for the 50 mg/kg group, suggesting that duration of eteplirsen therapy is more important than dose.
- The primary clinical endpoint of Study 202 was 6MWT change from baseline at 48 weeks. A difference between treatment groups was not observed, primarily due to 2 eteplirsen boys who experienced early loss of ambulation. Based on the evolving understanding that it may take 24 weeks of eteplirsen-treatment for significant dystrophin production, these 2 boys may have received eteplirsen too late in the course of their disease for an impact on the 6MWT. Notably, these two boys continue their participation in Study 202, receiving weekly eteplirsen treatment, and, as able, performing scheduled study assessments per protocol.
 - A descriptive analysis excluding these 2 boys was conducted. The remaining 10 ambulant eteplirsen treated boys performed better on 6MWT than placebo. Based on these encouraging, early results, Study 202 was extended.
 - The primary pharmacodynamic outcome, as measured by the percent dystrophin positive fibers at Week 48 was achieved.

- Additional clinical outcomes such as loss of ambulation (LOA), North Star Ambulatory Assessment (NSAA), pulmonary function tests (PFT), and other functional measures were collected through Year 4 for the 12 patients enrolled in Studies 201/202.

External Control Groups for Comparison to Eteplirsen

- The FDA requested that Sarepta obtain external control data from DMD registries with long-term 6MWT data for comparison to the long-term open-label eteplirsen data. After partnering with leading DMD experts, Sarepta identified 12 international DMD registries with clinical outcome data. Of these, 2 registries (Italian Telethon and Leuven Neuromuscular Research Center (LNMRC)) were identified to have available longitudinal 6MWT data. The Italian Telethon registry also had longitudinal NSAA data.
- The pre-specified criteria for identification of patients for the external control groups were based on the inclusion criteria for Study 201/202. These included baseline age, steroid use and specific DMD mutation. Each of these represent key prognostic factors that enable identification of a relatively homogenous population that would be expected to decline on the 6MWT.
- Application of these inclusion criteria to the two registries resulted in selection of the following external control groups:
 - A group with DMD mutations amenable to exon 51 skipping therapy (N = 13, primary external control group)
 - A larger group of boys with DMD mutations amenable to any kind of exon skipping therapy. This represents a more conservative control since it includes boys with milder phenotypes (N = 50, secondary external control group).

The primary basis for establishing the effectiveness of eteplirsen is a comparison of patients in Study 201/202 (N=12) to an untreated external control group amenable to exon 51 skipping (N=13)

Comparability of the Primary External Control Group to Eteplirsen Treated Patients

Following identification of the primary external control cohort, an analysis of key baseline characteristics confirmed the comparability of the eteplirsen and external control group on the key prognostic factors. In addition both groups of patients were treated according to harmonized international standards of care for DMD treatment including steroid use, physical therapy and use of orthotic devices.

Figure 1: Key Prognostic Factors Similar Between Eteplirsen Treated Patients (N=12) and External Controls Amenable to Exon 51 Skipping (N=13)

| Parameter | Eteplirsen Study 201/202 N=12 | External Control: Exon 51 Skip Amenable N=13 |
|--|--|---|
| Age, years | | |
| Mean (SD) | 9.4 (1.19) | 9.5 (1.45) |
| Median | 9.7 | 9.0 |
| Min, Max | 7.3, 11 | 7.3, 11.8 |
| 6MWT distance*, m | | |
| Mean (SD) | 363.2 (42.19) | 357.6 (66.75) |
| Median | 370 | 373 |
| Min, Max | 256, 416 | 200, 458 |
| Deletion mutations represented: | 45-50, 48-50, 49-50, 50, 52 | 45-50, 48-50, 49-50, 50, 52 |

*Day 1 values if tested more than once
All patients were on corticosteroids at baseline

Baseline characteristics for eteplirsen and untreated external control patients were comparable. In addition, important treatment factors were also similar, including longitudinal steroid use, physical therapy and use of orthotic devices. This is not unexpected, given that boys in the external control group were treated at leading neuromuscular clinics.

Eteplirsen Treatment Demonstrates an Effect on the “Intermediate” Clinical Endpoint 6MWT – That Is Reasonably Likely to Predict a Clinical Benefit

6 Minute Walk Test

Given the pivotal role of ambulation in daily human function and the impact of its inevitable loss in DMD, the 6MWT at Year 3 was agreed upon with FDA as the “intermediate” clinical efficacy outcome for Accelerated Approval. Subsequent to the NDA filing, Year 4 data were also requested by the Agency.

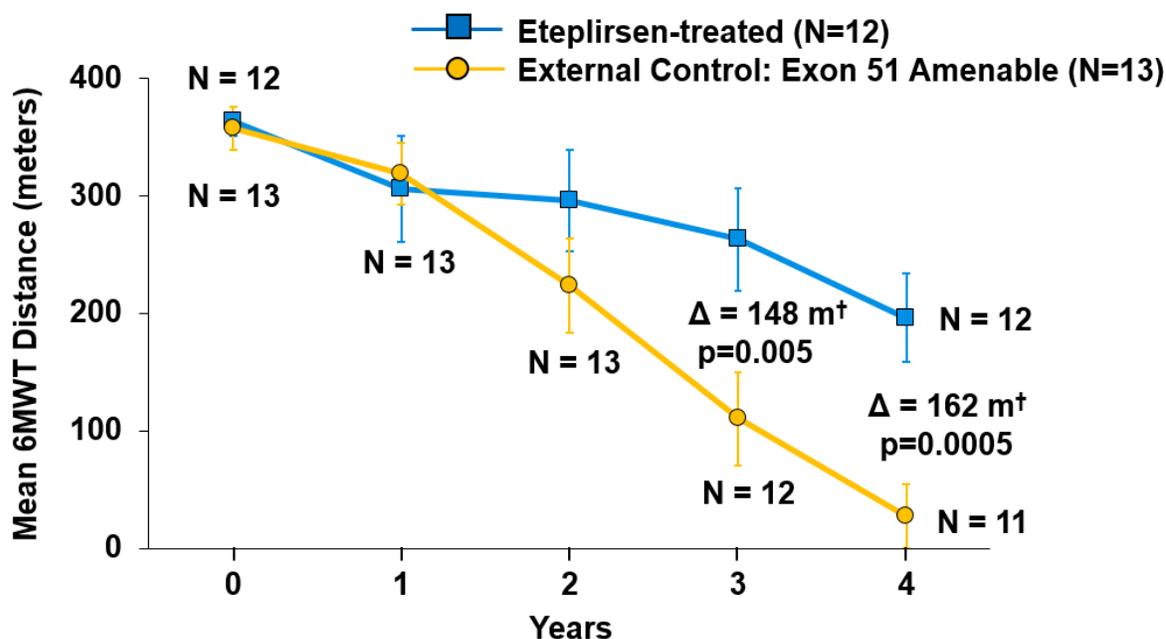
The 6MWT assessments in both Study 201/202 and the external registries were conducted in a standardized manner according to international guidelines.

Eteplirsen treated patients from pivotal Study 201/202 (N = 12) demonstrated a large magnitude of effect on the 6MWT, a 148 meter (p=0.005) advantage at Year 3, when compared to the external control (EC) group of similarly aged untreated boys with DMD mutations amenable to

exon 51 skipping (N = 13). This treatment effect manifested in a divergence of the trajectory of disease following the first year of eteplirsen therapy.

Based on the FDA request for Year 4 data, an updated analysis of 6MWT results through Year 4 was performed. This analysis demonstrates a sustained benefit for eteplirsen vs. the external control patients, with a 162 meter ($p=0.0005$) advantage at Year 4.

Figure 2: Mean 6MWT Values Over time in Eteplirsen Treated Patients vs External Control Amenable to Exon 51 Skipping



† Difference in mean change from baseline

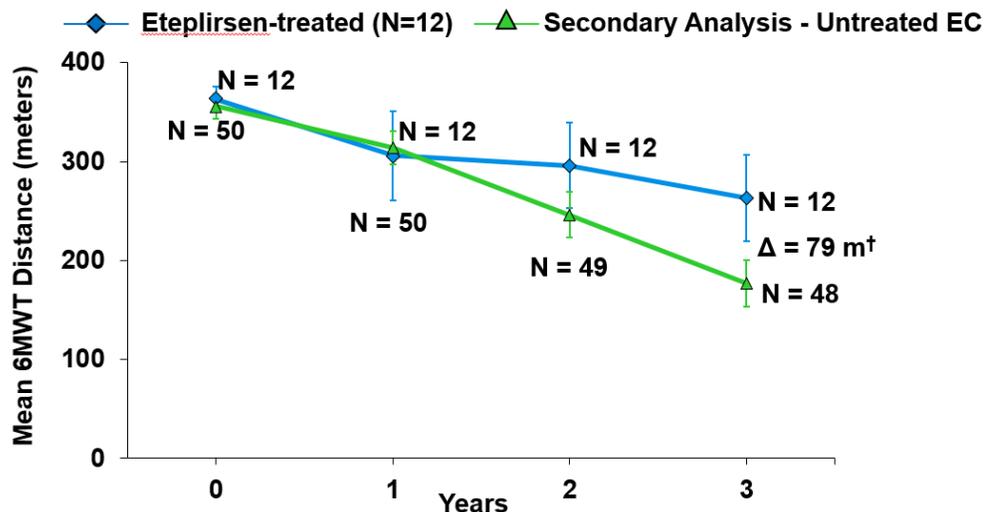
Patients who lost ambulation contributed a score of 0 to the mean

1 EC Subject was missing data at Year 3 & 4, 1 EC Subject was missing data at Year 4 only

A series of sensitivity analyses of the 4 year 6MWT results, including baseline covariates of age, 6MWT and steroid use, consistently demonstrated over a 100 meter treatment benefit for the eteplirsen treated group compared to the external control patients with exon 51 skippable mutations. Nominal p -values associated with the sensitivity analyses continued to be significant. Additional 6MWT information is provided in [Section 6.6.1](#).

In addition, a comparison of eteplirsen to the secondary external control group amenable to any exon skipping (N = 50) was conducted. Even though this larger group included 8 patients with a milder form of DMD amenable to exon 44 skipping ([Ricotti 2015](#)), there was still a substantive advantage of 79 meters ($p=0.062$) for patients treated with eteplirsen at Year 3.

Figure 3: Mean 6MWT Values Over time in Eteplirsen Treated Patients vs External Control Amenable to Any Exon Skipping



Eteplirsen treated boys (N=12) were able to walk 148 and 162 meters longer on the 6MWT at Years 3 and 4, respectively, than exon 51 amenable patients in the external control (N = 13). These results are both clinically relevant and statistically persuasive. The robustness of these findings is supported by sensitivity analyses and by comparisons to a larger, more conservative external control group amenable to any exon skipping (N = 50).

Loss of Ambulation

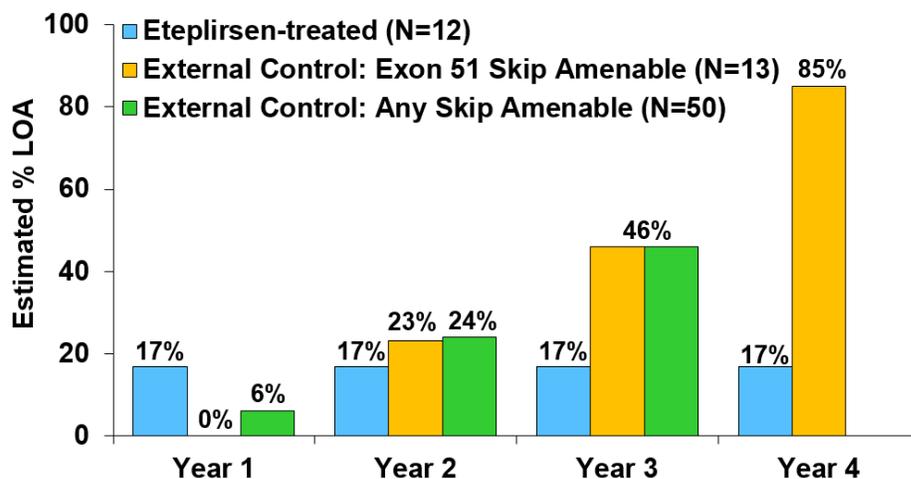
Ambulatory compromise and irreversible loss of ambulation (LOA) are hallmarks of the progressive muscle degeneration characteristic of DMD. It is a reliable overall indicator of the severity of disease progression and strongly correlates with functional measures such as the 6MWT; it is also less influenced by motivational factors. Furthermore, LOA predicts other major disease milestones such as the need for ventilatory support and survival (Bello 2016). Once confined to a wheelchair, other symptoms tend to follow in rapid succession. Consistent with results of the 6MWT, fewer eteplirsen treated boys lost ambulation (2/12) compared to the external control patients who were amenable to exon 51 skipping therapy (10/13) over the 4 year time period.

In addition, fewer eteplirsen treated boys lost ambulation (2/12) compared the external control group who were amenable to any type of exon skipping (18/50) over a 3 year time period.

Kaplan-Meier analyses for loss of ambulation were conducted, accounting for missing data. At Year 3 the estimated probability for loss of ambulation was 17% for eteplirsen treated boys compared to 46% of boys from both external control cohorts. At Year 4, Kaplan-Meier estimates of loss of ambulation was 17% for eteplirsen treated boys compared to 85% for the external

control boys amenable to exon 51 skipping. This difference in loss of ambulation over the 4-Year period was statistically significant, with a nominal p -value of 0.011. Additional loss of ambulation information is provided in [Section 6.6.2](#).

Figure 4: Kaplan-Meier Estimates of Loss of Ambulation Over 4 Years in Eteplirsen-Treated Patients vs. Primary External Control (N=13) and Over 3 Years vs. Secondary External Control



Eteplirsen’s treatment benefit on the delay of DMD progression as measured by the 6MWT is further confirmed by a reduction in the risk of Loss of Ambulation over a 4-year time period when compared to the external control group amenable to exon 51 skipping (17% vs 85%). This difference is accompanied by a statistically persuasive p -value of 0.011.

Supportive Endpoints: NSAA, Ability to Rise and PFTs Are Consistent with 6MWT

Northstar Ambulatory Assessment (NSAA)

The NSAA is a clinician-reported outcome instrument specifically designed to measure function in ambulatory patients with DMD. The 17 items are each scored on a 0-2 ordinal scale and include assessments of abilities such as rising from the floor, climbing and descending a step, 10 meter walk/run and lifting the head. Over the first year, both the eteplirsen treated boys and the Italian Telethon group declined at a similar rate. However, following Year 1, as was observed on 6MWT, the decline in function for the eteplirsen group slowed and by the end of Year 3 there was a 2.4 point greater decline for the untreated boys. This difference is of clinical relevance and may represent loss or impairment of up to 2 activities of daily living. Additional NSAA information is provided in [Section 6.6.3](#).

Ability to Rise without External Support

The ability to rise from supine is a critical activity for DMD patients, is one of the early abilities to be lost and may be predictive of loss of ambulation. In an analysis comparing the ability to rise from a supine position (without external support), 92% of eteplirsen treated vs 85% external control patients had the ability to rise without external support at baseline. By Year 3, 55% of eteplirsen vs 8% of external control patients had the ability to rise without external support.

It has been suggested by the FDA that the loss of ability to rise may predict loss of ambulation within 1-2 years. Following the FDA request for Year 4 data, an updated analysis of the relationship of ability to rise independently and loss of ambulation are provided in Section 6.6.4. Of note, 4 of the 10 ambulatory eteplirsen boys had lost the ability to rise independently from Years 1 to 3, yet all remained ambulatory at Year 4.

Pulmonary Function Tests

Respiratory function in DMD is progressively impaired over time as the dystrophic process affects respiratory muscles, including the diaphragm, leading to significant morbidity and mortality. Eteplirsen treated boys had slower deterioration of respiratory muscle function as measured by FVC %predicted (decrease of ~2.5% per year) when compared to data from the published literature ($\geq 5\%$ annual decline). Additionally, MEP %predicted and MIP %predicted may also decline more slowly with eteplirsen treatment than expected, although the scientific literature on these parameters is more limited. Additional respiratory function information is provided in Section 6.6.5.

Eteplirsen Treatment Demonstrates *de novo* Dystrophin Production, Confirming the Mechanism of Action

De novo Dystrophin Production

Eteplirsen is the first therapeutic to demonstrate an unequivocal increase in dystrophin following treatment.

In order to obtain a comprehensive view of dystrophin expression, biopsies were analyzed by three complementary assays. First, Western blot was used to quantitate dystrophin following extraction of protein from muscle tissue. Second, immunohistochemical (IHC) images were evaluated by trained, blinded pathologists to assess the percent dystrophin positive fibers (PDPF), providing information on sarcolemma localization and distribution of dystrophin in muscle fibers. Finally, the IHC images were also assessed by a computer algorithm to measure fiber intensity and to quantify dystrophin at the sarcolemmal membrane.

An 11.6-fold increase in *de novo* dystrophin production was observed by Western blot relative to untreated controls. This statistically significant fold increase was confirmed in both IHC assays, as highlighted by the Week 180 biopsy results detailed in Table 1. As expected based on literature (Anthony 2014b, Taylor 2012), a strong correlation was seen between fiber intensity and Western blot (Pearson Correlation Coefficient = 0.709; p-value = 0.015).

The sustained production of *de novo* dystrophin at Week 180 can only be attributed to drug treatment, providing strong and direct support for eteplirsen's mechanism of action.

Significant dystrophin production was demonstrated by all three methods including IHC and Western Blot.

Table 1: Week 180 Biopsy Results

| Week 180 Dystrophin Assay | Untreated (Mean % Dystrophin of Normal) | Treated (Mean % Dystrophin of Normal) | Difference of Means (Treated vs. Untreated) | p-Value | Fold Increase |
|---------------------------|---|---------------------------------------|---|---------|---------------|
| IHC: PDPF | 1.12% | 17.39% | +16.27% | <0.001 | 15.5 |
| IHC: Intensity | 9.41% | 22.61% | +13.20% | <0.001 | 2.4 |
| Western Blot | 0.08% | 0.93% | +0.85% | 0.007 | 11.6 |

Eteplirsen unequivocally demonstrated production of *de novo* dystrophin by all 3 methods studied, highlighted by an 11.6 fold increase from baseline on Western Blot.

Relationship of Dystrophin to DMD Severity

Although a linear correlation between the amount of dystrophin and clinical course has not been established, it is clear that the presence of some dystrophin results in disease amelioration. The clinical literature demonstrates that the presence of low or trace levels of dystrophin result in a milder disease course. In particular, patients amenable to exon 44 skipping have been shown to express higher, albeit trace levels of dystrophin than are typically seen in DMD patients. These patients experience a milder disease course compared to other types of DMD (Anthony 2014a). In a recent large prospective DMD natural history study (CINRG), an approximate 2-year delay of median loss of ambulation was observed in 20 participants who had mutations amenable to exon 44 skipping. (Bello 2016).

Safety

The safety profile of eteplirsen has been characterized in 114 patients with DMD mutations amenable to exon 51 skipping participating in 7 clinical studies (Section 9.2). Eighty-eight (88) patients received doses of 30 mg/kg or higher, including 61 patients treated for at least 3 months. Safety monitoring has included frequently scheduled clinical and/or laboratory assessments and review of adverse events (AEs) for infusion reactions, renal toxicity, hepatotoxicity, coagulopathy, cutaneous reactions and cardiac-related events with no apparent signal for significant safety risks.

Eteplirsen is well tolerated as evidenced by the low rates of serious or severe adverse events, or adverse events leading to discontinuation of study drug.

- The favorable tolerability of eteplirsen is demonstrated by low rates of treatment emergent SAEs (N = 2; 1.8%) and AEs resulting in study drug discontinuation (N = 1; 0.9%).

- The most common ($\geq 10\%$ of patients) TEAEs occurring more frequently in patients treated with eteplirsen at either 30 or 50 mg/kg IV than in patients who received placebo were: headache, arthralgia, vomiting, upper respiratory tract infection, nasopharyngitis, cough, nasal congestion, contusion, excoriation and procedural pain.
 - The majority of events were mild and resolved with ongoing study drug.
 - Many events may be reflective of the types of conditions that occur in a pediatric population with DMD.
- Three mild events were considered potential adverse drug reactions due to the temporal relationship with eteplirsen administration: erythema, flushing, and mild temperature elevation.
- Adverse Events of Special Interest (i.e., coagulopathy, infusion site and infusion-related reactions, severe cutaneous reactions, hypersensitivity, leukopenia, cardiac, renal and hepatic function) and related laboratory parameters were reviewed and no apparent safety signal was detected.

The safety profile of eteplirsen, based on 114 patients, is tolerable with no apparent signal for major safety risks.

Confirmatory Studies to Verify the Clinical Benefit of Eteplirsen

Sarepta is committed to the completion of confirmatory trials that will not only verify the clinical benefit of eteplirsen using the 6MWT and other functional endpoints, but will also contribute additional data to the safety profile of eteplirsen.

PROMOVI is an open label confirmatory study evaluating the clinical outcomes and safety of eteplirsen in a population of DMD boys who are amenable to exon 51 skipping compared to an untreated control group of patients with DMD who are amenable to any exon (non-51) skipping. PROMOVI was designed in consultation with FDA and reflects feedback from the DMD community indicating that a placebo controlled trial of eteplirsen would not be feasible.

ESSENCE is a planned double blind placebo controlled confirmatory study that will evaluate the efficacy of PMOs that are designed for the treatment of DMD mutations that are amenable to either exon 45 or 53 skipping. These PMOs have the same chemical backbone and mechanism of action as eteplirsen. The clinical course of patients amenable to exon 45 and 53 skipping is similar to that of exon 51 skipping amenable patients ([Bello 2016](#)).

Favorable Benefit Risk Profile of Eteplirsen

The benefits of eteplirsen treatment have been demonstrated by multiple clinical and pharmacodynamic endpoints.

- Large magnitude of effect on 6MWT, that is clinically meaningful and statistically persuasive
 - 148 meter benefit at Year 3 (p=0.0052)
 - 162 meter benefit at Year 4 (p=0.0005)

- Significant benefit on the loss of ambulation
 - 17% vs 85% probability of losing ambulation at Year 4
(Kaplan-Meier analysis, p-value = 0.011)
- Supportive endpoints directionally consistent: NSAA, ability to rise and PFTs
- Mechanism of action and production of *de novo* dystrophin demonstrated

In addition, the safety profile of eteplirsen, based on 114 patients, is tolerable with no apparent signal of significant safety risks observed.

Eteplirsen offers patients with DMD, an unparalleled opportunity for delayed disease progression and loss of ambulation. The benefits of eteplirsen, when weighed against the certainty of relentless disease progression in DMD, justify the accelerated approval of eteplirsen in the treatment of DMD amenable to exon 51 skipping therapy.

2. OVERVIEW OF DUCHENNE MUSCULAR DYSTROPHY (DMD)

2.1. Onset and Progression

Duchenne muscular dystrophy (DMD) is a rare, serious, life threatening, degenerative neuromuscular disease with a recessive X-linked inheritance. Caused by mutations in the dystrophin gene, DMD is characterized by the absence, or near absence, of functional dystrophin protein, leading to relentlessly progressive deterioration of skeletal muscle function from early childhood, and premature death, usually by 30 years of age.

The progression of DMD follows a predictable course. Biochemical and molecular evidence of myofiber membrane instability are typically evident from shortly after birth (Chen 2005); however, clinical manifestations of ongoing muscle damage are usually obscured by otherwise normal growth and maturation during infancy. In fact, initial symptoms of DMD are often not reported until 2-3 years of age, with patients being diagnosed, on average at approximately 4 to 5 years of age (Bushby 2010a; Ciafaloni 2009; van Ruiten 2014). Initial symptoms of DMD most often include waddling gait, toe walking, falls, and delayed speech (Ciafaloni 2009; van Ruiten 2014). Compared with healthy, same-age peers, the achievement of motor milestones in patients with DMD is delayed, and performance on tests of motor function, such as timed function tests, is markedly impaired (Beenakker 2005; McDonald 2010a; McDonald 2010b).

Functional improvements due to natural growth are observed heterogeneously in boys younger than age 7, until the characteristic degeneration and loss of muscle tissue outpaces maturational development and physical growth (McDonald 2010b; Mazzone 2013). At 7 years of age the disease trajectory for DMD has been observed to decline in a relentless and progressively precipitous fashion. Once this threshold is crossed, disease trajectory is predictively negative and 6MWD decreases more rapidly each year (Mendell 2016; Mazzone 2013; Pane 2014b). At this time, DMD boys who were steadily gaining in physical function, albeit at a slower rate than their healthy age-matched peers, begin a progressive decline. This age dichotomy is supported by literature; in a 3 year longitudinal dataset boys who entered into observation prior to age 7 demonstrated improvement for the first two years, with decline observed by the third year when the mean age of the cohort was over 8 years (Pane 2014b; Mendell 2016).

By 8 years of age, most DMD patients lose the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking. By 10 to 14 years of age, most have become wheelchair dependent. Once confined to a wheelchair, other symptoms tend to follow in rapid succession. There is gradual loss of upper limb, trunk, and neck function, such that self-grooming, toileting, bathing, dressing, unsupported sitting, and eating become impaired or impossible, severely affecting patient quality of life, as well as that of caregivers and families (Bendixen 2012; Bendixen 2014; Buyse 2012; Buyse 2015; Hahn 1997; Magliano 2014; Uzark 2012).

While few, if any, respiratory symptoms have been reported in the earliest stages of DMD, data from recent natural history studies in patients with DMD suggest that from the time pulmonary function testing (PFT) is first performed, usually at the ages of 4 or 5 years, percent predicted values for forced vital capacity (FVC) and maximum inspiratory (MIP) and expiratory (MEP) pressures decline (Khirani 2014; Mayer 2015). Diaphragmatic muscles progressively weaken

during adolescence, and patients often require ventilation support in their mid to late teens (Bushby 2010a; Bushby 2010b).

There is also an increased risk of cardiomyopathy with DMD (Thomas 2012), which usually manifests after 10 years of age as dilated cardiomyopathy with reduced left ventricular ejection fraction. The prevalence of cardiomyopathy has been shown to increase with age and disease progression, with 10% to 20% of patients affected between 6 and 13 years of age and over 60% of patients ≥ 18 years affected (Spurney 2014). Historically, patients with DMD died from respiratory or cardiac failure in their late teens or early 20s (Brooke 1989; Eagle 2002). Although recent studies suggest that use of ventilation support, steroids, surgery, diet and other supportive measures may increase life span by several years (Kohler 2009; Bushby 2010a; Bushby 2010b; Moxley 2010), DMD remains fatal by early adulthood.

2.2. Diagnosis and Determination of Mutation

Historically, diagnosis of DMD had to be confirmed by muscle biopsy; however, genetic testing for DMD has become a common part of the diagnostic process in treatment centers in the US and Europe, thereby reducing the need for muscle biopsies. The use of newer methods of testing, such as next generation sequencing, has greatly improved the sensitivity and accuracy of genetic testing for DMD and ensures that patients amenable to exon 51 skipping can be readily and reliably identified (Wei 2014; Bovolenta 2012). Importantly, in the US, even patients and families lacking or having insufficient insurance coverage are able to access genetic testing for DMD at no cost through the “Decode Duchenne” program, which was launched by Parent Project Muscular Dystrophy (PPMD).

2.3. Current Treatments for DMD and Unmet Medical Need

There is no approved therapy for DMD in the US. Currently, uniform standard of care guidelines for treatment of patients with DMD in the US and Europe include the administration of glucocorticoids in conjunction with nutritional, orthopedic, respiratory, cardiac, pain, psychosocial, and other palliative interventions (Bushby 2010a; Bushby 2010b). Aside from glucocorticoids, none of these interventions have been shown to impact loss of ambulation. Although glucocorticoids can delay the loss of ambulation as well as the onset of respiratory dependence, scoliosis, and cardiomyopathy (Beenakker 2005; Biggar 2006; Pradhan 2006; Manzur 2009; Schram 2013; Henricson 2013a), they do not sufficiently ameliorate symptoms or address the underlying genetic mutation and lack of functional dystrophin. Moreover, glucocorticoid use is often limited by numerous side effects, including weight gain, behavioral changes, hypertension, hyperglycemia and osteoporosis. Thus, there remains a high unmet medical need for treatments for patients with DMD.

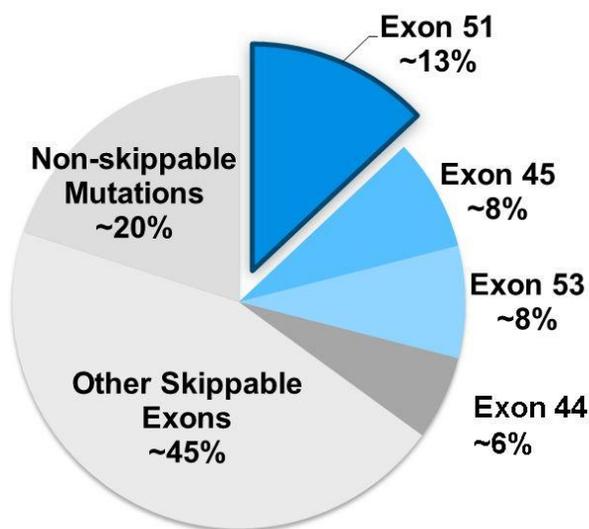
2.4. Epidemiology

The worldwide incidence of DMD is 1 in 3,500-5,000 newborn boys, irrespective of geographical region, race, or population density (Zaharieva 2013; Mendell 2012; Moat 2013). The prevalence of DMD in the United States (US) is estimated to be approximately 9,000 to 12,000. The most common cause of DMD is deletion mutations of one or more DMD exons, accounting for approximately two-thirds of DMD cases (Aartsma-Rus 2009; Bladen 2015). Approximately 13% of all DMD patients have mutations amenable to therapies that skip

exon 51, corresponding to approximately 1,300-1,900 patients in the US who would potentially benefit from exon 51 skipping therapy (Figure 5). Another 16% percent have mutations amenable to treatment by skipping exons 45 (8%) and 53 (8%), and an additional 51% have mutations amenable to treatment by skipping other exons. Thus, hypothetically, exon skipping PMO therapies could potentially address treatment needs for approximately 80% of all DMD mutations.

Figure 5: US Prevalence of Patients with Exon 51 Skippable Deletions and other DMD Mutations

- ◆ **US prevalence of DMD: 9,000 to 12,000 boys**
- ◆ **~13% of DMD patients amenable to exon 51 skipping**



Source: Adapted from [Aartsma-Rus 2009](#).

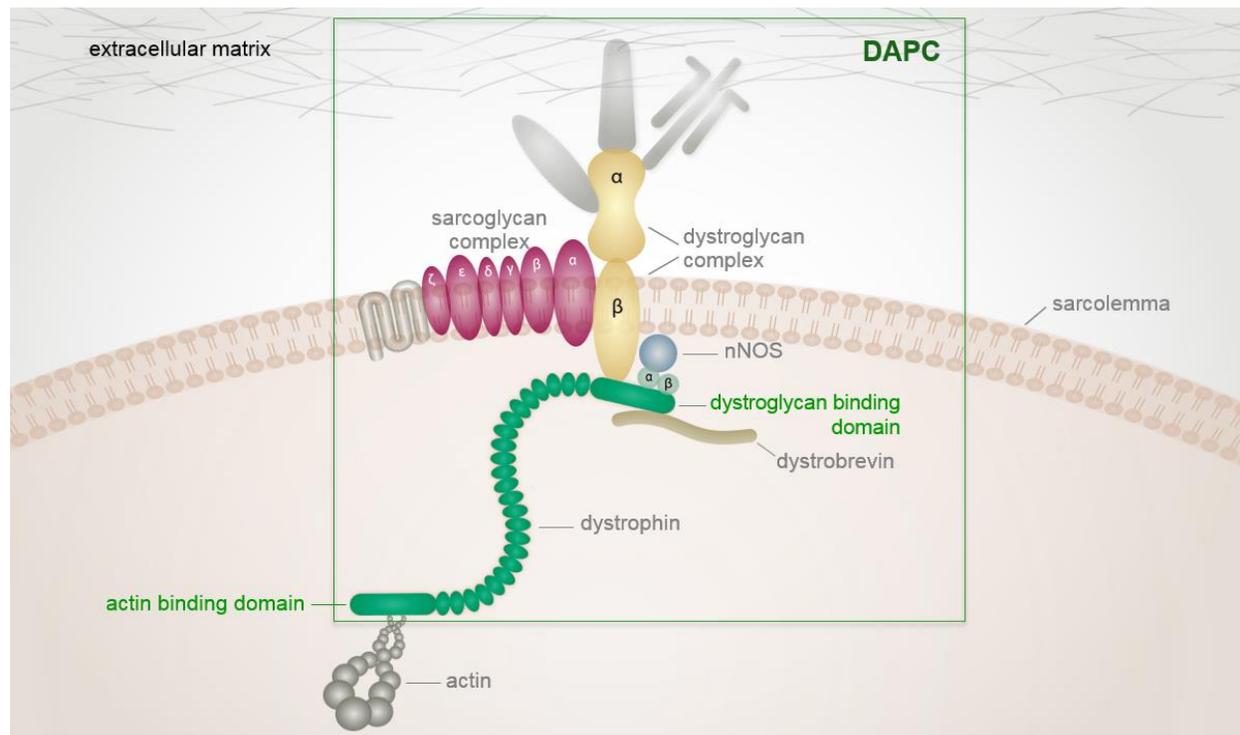
2.5. Pathophysiology and Role of Dystrophin

2.5.1. Dystrophin in Normal Muscle

Dystrophin is a low abundance (<0.1%) protein in muscle tissue with a slow translation time (~16 hours) and low turnover (half-life of ~2 months) ([Wu 2012](#); [Tennyson 1995](#); [Hoffman 1987](#)).

Dystrophin is a critical structural protein that protects muscle from strain-induced injury. Often referred to as a “molecular shock absorber”, dystrophin links the intracellular actin filaments of a muscle fiber to the cell membrane and surrounding extracellular matrix through its interaction with the dystrophin-associated protein complex (DAPC). Dystrophin binds directly to cytoplasmic actin through its *N-terminal actin-binding domain* and localizes to the sarcolemma and the DAPC via its *C-terminal dystroglycan binding domain* ([Figure 6](#)). Together, dystrophin and the other components of the DAPC protect muscle from the forces of repeated contraction and relaxation ([Kobayashi 2012](#)).

Figure 6: The DAPC in Normal Muscle



Abbreviations: DAPC = dystrophin associated protein complex.
Adapted from Kobayashi 2012.

2.5.2. Dystrophin Protein in DMD and BMD

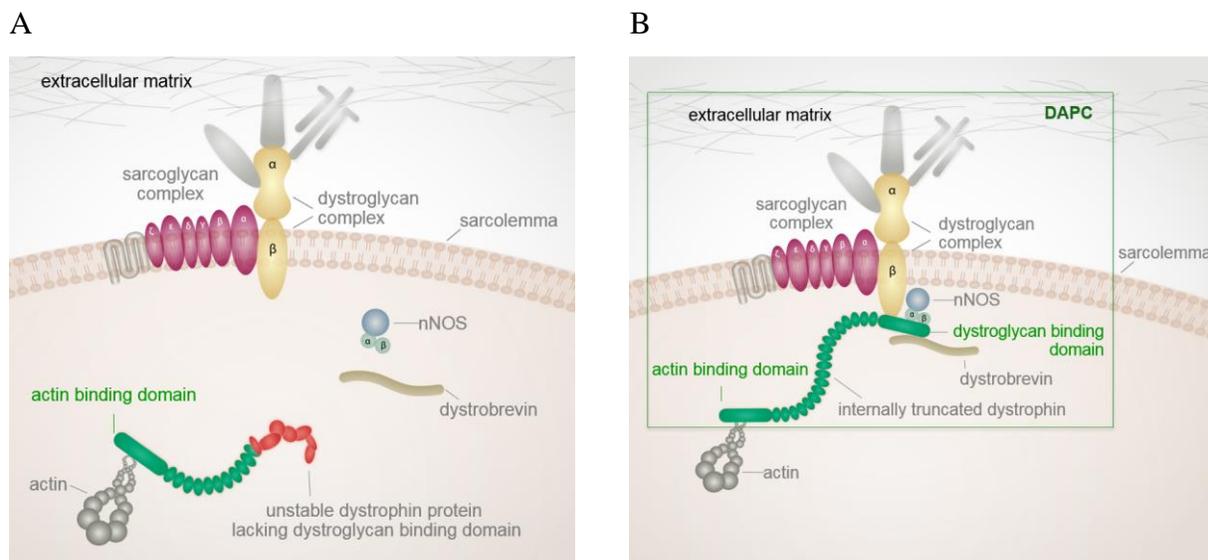
Mutations in the gene encoding dystrophin give rise to a spectrum of neuromuscular disorders called dystrophinopathies. The most common mutations are whole exon deletions, which, depending on the exon(s) deleted, result in severe and fatal DMD or the significantly milder dystrophinopathy, Becker muscular dystrophy (BMD).

Whole exon deletions that disrupt the mRNA reading frame, also referred to as “out-of-frame deletions” are the primary cause of DMD. Out-of-frame mutations prevent translation of functional dystrophin protein downstream of the mutation, creating an unstable protein lacking a *C-terminal dystroglycan binding domain* (Figure 7A). The absence of functional dystrophin prevents the connection between the intracellular cytoskeleton and the cell membrane leading to repeated cycles of cellular inflammation, degeneration, and cumulative damage to muscle. Over the clinical course of DMD, the inherent ability of muscle cells to repair and regenerate is exhausted and muscle is progressively replaced by fibrotic tissue and fat (Blake 2002; Emery 2002).

In contrast, whole exon deletions that do not disrupt the mRNA reading frame, also referred to as “in-frame deletions”, are usually associated with BMD. Such mutations result in a dystrophin protein missing amino acids in the central domain; however, the C- and N-terminal binding domains are retained. (Figure 7B). Due to this preservation of functional dystrophin, BMD

patients generally have a much later onset of symptoms, a milder and slower disease course, and a near normal life expectancy (McDonald 1995; Bushby 1993a; Bushby 1993b; Kaspar 2009).

Figure 7: The DAPC in DMD (A) and BMD (B) Muscle



Adapted from Kobayashi 2012.

2.5.3. Relationship of Dystrophin to DMD and BMD Severity

A linear relationship between dystrophin expression and clinical course of dystrophinopathies has not been established (Hoffman 1988; Bushby 1993b; Bushby 1992; Taylor 2012; Nicholson 1993; Hoffman 1989; Anthony 2014a; van den Bergen 2014; Goldberg 1998; Lenk 1996).

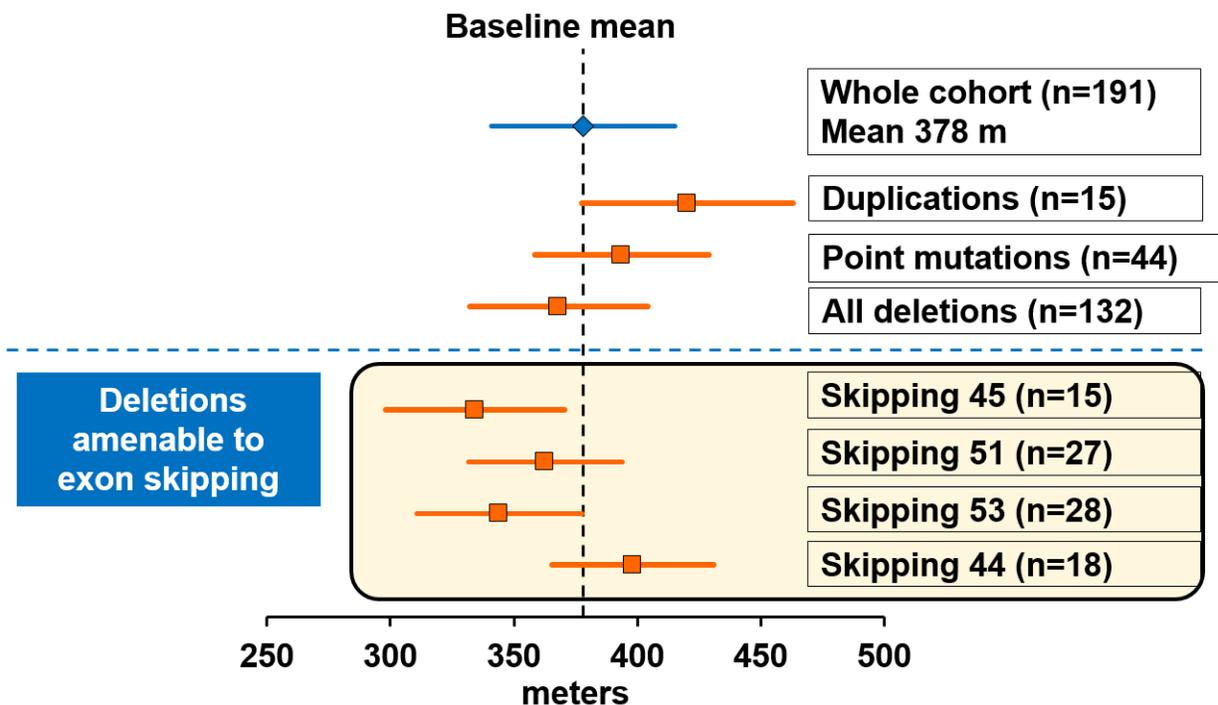
Dystrophin levels, while lower overall in patients with DMD, were highly variable among both DMD and BMD patient groups, and do not appear to correlate linearly with disease severity. In BMD, expression of dystrophin by Western Blot has been variable with estimates from the literature ranging from 2%-100% of normal muscle levels leading one publication to posit that the presence of a relatively small amount of dystrophin may be sufficient to result in a disease course that is milder than DMD (van den Bergen 2014).

The clinical literature demonstrates that the presence of low or trace levels of dystrophin result in a milder disease course. Some DMD patients with certain mutation types express very low levels of dystrophin attributable to naturally occurring, spontaneous exon skipping. The sporadic muscle fibers expressing dystrophin are referred to as “revertant” fibers. In particular, patients amenable to exon 44 skipping have been shown to express higher, albeit trace levels of dystrophin than are typically seen in DMD patients due to the phenomenon of naturally occurring revertant muscle fibers (Anthony 2014a, Bello 2016).

Corresponding to the presence of low levels of dystrophin, patients with DMD mutations amenable to skipping exon 44 experience a milder disease course compared to other types of DMD (Anthony 2014a). In a recent large prospective DMD natural history study (CINRG), an approximate 2-year delay of median loss of ambulation was observed in 20 participants who had

mutations amenable to exon 44 skipping. (Bello 2016). A second study conducted in a cohort of 191 similarly-aged boys with DMD (Pane 2014a) examined the relationship between DMD genotypes and distance walked on the 6-Minute Walk Test (6MWT). Patients amenable to exon 44 skipping walked further (a mean distance of 398 meters) compared to boys with DMD amenable to skipping exons 45, 51, and 53 who walked mean distances of 334, 362, and 344 meters, respectively (Table 4). A third study of 513 steroid treated boys with DMD also demonstrated that exon 44 amenable patients declined at a slower rate than the overall DMD population over 24-months on the North Star Ambulatory Assessment (NSAA) ($p < 0.01$) (Ricotti 2015).

Figure 8: Comparison of 6MWT Performance in Patients with DMD Mutations Amenable to Exon Skipping



Source: Adapted from: Pane 2014a. This figure shows mean distance walked on the 6MWT in patients with different DMD mutations relative to the mean distance walked by the whole cohort.

In summary, published literature demonstrates that the presence of even low levels of functional dystrophin results in milder disease course in patients with BMD and in patients with DMD mutations amenable to exon 44 skipping. Although a linear correlation between the amount of dystrophin and clinical course has not been established, it is clear that the presence of some dystrophin results in disease amelioration.

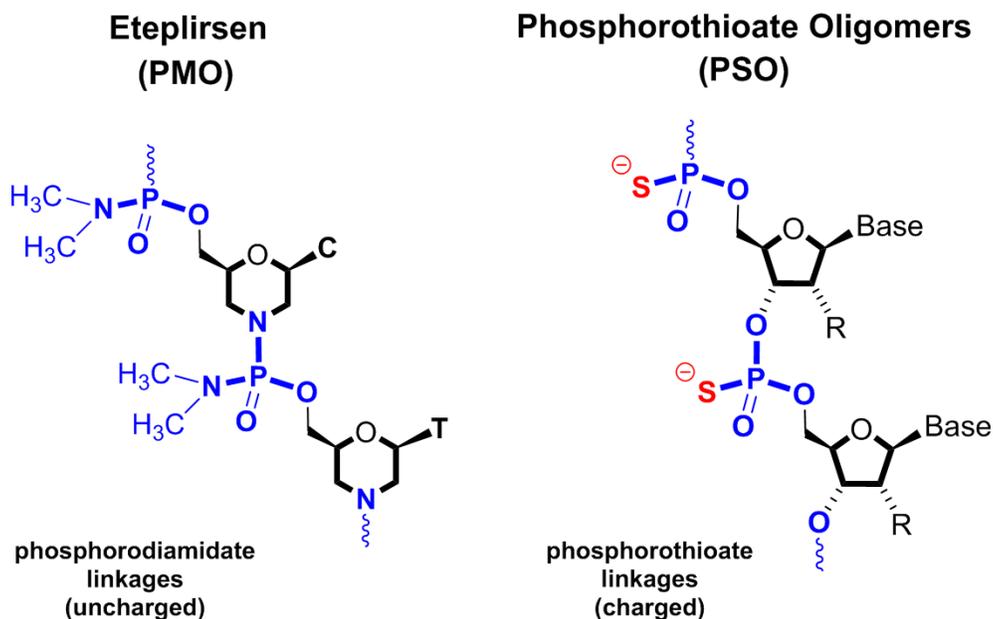
3. ETEPLIRSEN DEVELOPMENT

3.1. Background Information on Eteplirsen Injection

Eteplirsen belongs to a distinct class of novel synthetic antisense RNA therapeutics called Phosphorodiamidate Morpholino Oligomers (PMO), which are a redesign of the natural nucleic acid structure (Figure 9). PMOs offer potential clinical advantages based on *in vivo* nonclinical observations.

- PMOs incorporate modifications to the sugar ring of RNA that protect it from enzymatic degradation by nucleases in order to ensure stability *in vivo*. PMOs are distinguished from natural nucleic acids and other antisense oligonucleotide classes in part through the use of 6-membered synthetic morpholino rings, which replace the 5-membered ribofuranosyl rings found in RNA, DNA and many other synthetic antisense RNA oligonucleotides.
- The uncharged phosphorodiamidate linkages specific to PMOs are considered to potentially confer reduced off-target binding to proteins. PMOs have an uncharged phosphorodiamidate linkage that links each morpholino ring instead of the negatively charged phosphorothioate linkage used in other clinical-stage synthetic antisense RNA oligonucleotides.
- The sequence of eteplirsen's 30 nucleobases is designed to be complementary to a specific target sequence within exon 51 of dystrophin pre-mRNA. Each morpholino ring in eteplirsen is linked to one of four heterocyclic nucleobases found in DNA (adenine, cytosine, guanine, and thymine).

Figure 9: Phosphorodiamidate Morpholino Oligomer Structure (vs Phosphorothioate)



The chemical name for eteplirsen is:

RNA, [P-deoxy-P-(dimethylamino)] (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a→ 5') (C-m⁵U-C-C-A-A-C-A- m⁵U-C-A-A-G-G-A-A-G-A- m⁵U-G-G-C-A- m⁵U- m⁵U- m⁵U-C- m⁵U-A-G), 5'-[P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl]-N,N-dimethylaminophosphonamidate]

Note “m⁵U” stands for 5-methyluracil (i.e., thymine).

3.2. Rationale for Development and Mechanism of Action

A potential therapeutic approach to the treatment of DMD caused by out-of-frame mutations in the *DMD* gene is suggested by the milder form of dystrophinopathy known as BMD, which is caused by in-frame mutations. The ability to convert an out-of-frame mutation to an in-frame mutation would hypothetically preserve the mRNA reading frame and produce an internally shortened yet functional dystrophin protein. Eteplirsen was designed to accomplish this.

Eteplirsen targets dystrophin pre-mRNA and induces skipping of exon 51, so it is excluded or skipped from the mature, spliced mRNA transcript. By skipping exon 51, the disrupted reading frame is restored to an in-frame mutation. While DMD is comprised of various genetic subtypes, eteplirsen was specifically designed to skip exon 51 of dystrophin pre-mRNA. DMD mutations amenable to skipping exon 51 include deletions of exons contiguous to exon 51 (i.e. including deletion of exon 50 or exon 52), and comprise the largest subgroup of DMD patients (13%).

Eteplirsen is an antisense RNA therapeutic-targeted with a nucleobase sequence that is complementary to a specific sequence contained within exon 51 of dystrophin pre-mRNA. Hybridization of eteplirsen with the targeted pre-mRNA sequence interferes with formation of the pre-mRNA splicing complex and deletes exon 51 from the mature mRNA. The structure and conformation of eteplirsen allows for sequence-specific base pairing to the complementary sequence contained in exon 51 of dystrophin pre-mRNA as illustrated by [Figure 10](#).

Eteplirsen skips exon 51 to restore the mRNA reading frame. Since exon 49 ends in a complete codon and exon 52 begins with the first nucleotide of a codon, deletion of exon 51 restores the reading frame, resulting in production of an internally-shortened dystrophin protein with an intact dystroglycan binding site, similar to an “in-frame” BMD mutation.

Figure 13: Depiction of Eteplirsen Restoration of “In-frame” reading of pre-mRNA



Source: Adapted from Kole 2012.

3.3. Proposed Indication, Dosing and Administration

The proposed prescribing information for eteplirsen includes the following indication:

Eteplirsen injection is indicated for the treatment of DMD in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping therapy. This indication is approved based on an intermediate endpoint demonstrating delayed disease progression as measured by the 6MWT. Continued clinical benefit will be evaluated through confirmatory trials.

Eteplirsen injection is supplied in single-use, 2- and 10-mL glass vials containing 100 or 500 mg eteplirsen, respectively. The concentrated drug product is provided as a 50 mg/mL sterile, isotonic, phosphate-buffered (pH 7.5) solution without preservatives. Eteplirsen injection is diluted to 100 to 150 mL with normal saline prior to administration via intravenous (IV) infusion.

Eteplirsen at 30 mg/kg will be administered chronically (i.e., lifetime dosing) by once-weekly IV infusions between 35 to 60 minutes in duration.

3.4. Regulatory History and Framework

Sarepta Therapeutics (Sarepta) is seeking accelerated approval (AA) for eteplirsen administered as weekly 30 mg/kg IV infusions for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping therapy.

The primary basis for establishing the effectiveness of eteplirsen is a comparison of patients in Study 201/202 (N=12) to an untreated external control group amenable to exon 51 skipping (N=13).

Sarepta and the FDA have no more critical challenge than to reliably bridge and extend the benefits of medical innovation to patients. Eteplirsen has been developed as an innovative therapy, customized to treat a unique set of DMD genetic mutations, those which are amenable to skipping exon 51.

3.4.1. Regulatory Framework

FDA's existing authority allows for the use of scientifically-driven flexibility in the application of the statutory standards for approval, in particular through the accelerated approval pathway for serious or life-threatening diseases as codified in the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on 09 July 2012. While application of regulatory flexibility has been most prevalent in the areas of oncology and HIV/AIDS, nowhere is the use of such flexibility more impactful than in the case of new therapies for the treatment of serious and life-threatening rare diseases. The need for innovative and flexible approaches to FDA review across divisions increases as more rare disease therapies are being developed, where the contextual knowledge of patients and their diseases often evolves in parallel with clinical development.

Authority for such flexibility is borne directly from federal regulations which state in part “[w]hile the statutory [substantial evidence of effectiveness] standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards.” The regulations go on to empower use of this flexibility by requiring the FDA “*to exercise its scientific judgment to determine the kind and quantity of data and information... required to provide for a particular drug to meet the statutory standards*” (21 CFR 314.105(c)). More recently, FDA affirmed in draft guidance that “[t]here is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease.” (Guidance for Industry - *Rare Diseases: Common Issues in Drug Development*, August 2015). Importantly, FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards for new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists (21 CFR §312.80).

Congress embraced this flexible approach to drug evaluation in enacting Title IX of FDASIA in 2012. That law provided both the Findings and Sense of Congress with respect to FDA's authority to grant accelerated approval for drugs for serious and life-threatening diseases where the effect on a surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit. Specifically, Congress emphasized that:

... “the FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate.”

Uncertainty about whether clinical benefit would be verified and the possibility of undiscovered risks are the reasons that accelerated approval is reserved for drugs intended to treat serious conditions, such as the use of eteplirsen in the treatment of Duchenne muscular dystrophy. Importantly, FDA acknowledged that approval under such a pathway may involve “*fewer, smaller, or shorter clinical trials than is typical for a traditional approval...*” (FDA Guidance for Industry: *Expedited Programs for Serious Conditions – Drugs and Biologics*, May 2014) and that “*trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support*

approval.” (FDA Guidance for Industry: *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment*, June 2015).

There are numerous examples where FDA’s flexibility has established regulatory precedent in rare diseases, including those described below:

- Myozyme (alglucosidase alfa): approved in August 2014 for the treatment of patients with infantile onset Pompe disease. The approval precedent reflects the use of a natural history database to create a subgroup-matched historical control, selecting patients from the broader population with efficacy that meet certain prognostic factors (e.g., age, age of onset, documented phenotype).
- Carbaglu[®] (carglumic acid): approved in March 2010 for treatment of N-acetylglutamate synthase (NAGS) deficiency based on a case series from fewer than 20 patients and comparison to a historical control group.
- Ceptrotin[®] (human plasma derived protein C concentrate): approved in March 2007 for the treatment of severe congenital Protein C deficiency based on a study of 18 patients using a comparison to historical control data.

Such variation in the type and quantity of evidence used by the FDA to assess the efficacy of novel therapeutic agents underscores the Agency’s flexible approach to meeting standards for drug approval. It is clear in the context of the review of drugs for rare diseases that FDA has the authority—and specific direction from Congress—to exercise flexibility in considering all of the available data.

3.4.2. Eteplirsen Regulatory History

The eteplirsen IND was submitted in August 2007 for the treatment of DMD patients with mutations amenable to exon 51 skipping therapy. Orphan Drug and Fast Track designations were also granted for eteplirsen for this indication in October and November 2007, respectively. Based on promising results observed in the Phase 1 proof of concept study (Study 33) and a 12 week dose-ranging study (Study 28) conducted in the United Kingdom from 2007 to 2010, Sarepta conducted a 28-week double-blind, placebo-controlled Phase 2 study (Study 201) in July 2011. In February 2012, a long-term Phase 2b open-label eteplirsen extension study (Study 202) was initiated where all 12 patients who participated in Study 201 received eteplirsen. Study 202 has now been ongoing for approximately 4 years.

Based on the regulatory framework of FDASIA and after several meetings with the Division of Neurology Products, agreement was reached on the content of an NDA submission, primarily based on the Phase 2b dataset, for review under the provisions of 21 CFR §314.510 (Subpart H) regulations established for accelerated approval of new drugs for serious or life-threatening illnesses, and confirmatory study design.

Of note, the FDA requirements for Accelerated Approval (AA) are detailed in [Table 2](#). In addition, “the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments need to be taken into account. Post marketing confirmatory trials are required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.” The eteplirsen NDA submission meets the criteria for accelerated approval.

Table 2: Eteplirsen Meets Accelerated Approval Requirements

| Characteristics | Accelerated Approval Section 506 (c) | Eteplirsen Pathway |
|--|--|--|
| Disease | Serious, life-threatening Severe or rare Lack of alternative treatments | Duchenne Muscular Dystrophy |
| Surrogate or “intermediate” clinical endpoint | <i>Reasonably</i> likely to predict clinical benefit | Intermediate clinical endpoint: 6MWT (primary comparison) |
| Post-marketing (PM) studies | PM confirmatory trials required to verify and describe anticipated effect | Two confirmatory studies |

FDA Meeting Minutes Received April 2014 (Culmination of 4 meetings held between November 8, 2013 and March 2014)

The FDA provided the following guidance:

- The FDA outlined 2 potential pathways to accelerated approval:
 1. *“Considering the 201/202 6MWT data as a finding on an “intermediate” clinical endpoint, or”*
 2. *“Using the dystrophin biomarker data as surrogate endpoint(s)”*
- For option (1), Sarepta 201/202 6MWT data would need to be compared to a matched historically-controlled DMD population similar to the eteplirsen treated patients; patient-level data would need to be submitted for both groups. In order to minimize bias, the supportive care, such as steroid use and physical therapy, for both groups would need to be similar.
- The FDA remained “skeptical” about the persuasiveness of the existing biomarker data as it had been analyzed by a single pathologist and therefore potentially open to bias. FDA proposed a collaborative effort to better understand the methods and analyses used for these data, with the goal of applying suitable, consistent, and objective methods for measuring increases in functional dystrophin protein, which would be amenable to independent verification.
- The FDA also proposed obtaining a fourth biopsy and comparing these samples, in blinded fashion, to samples obtained from a group of treatment-naïve patients with exon 51 DMD, as a source of additional biomarker data.

Confirmatory Studies

To enable accelerated approval, the “FDA envisioned 2 approaches to confirmatory trials:”

1. “A historically-controlled trial of eteplirsen, and
2. A randomized, placebo-controlled trial of another PMO with the same mechanism of action, with demonstration of a correlation between dystrophin production and definitive clinical benefit on the 6MWT or another clinical measure.”

September 2014: Type B Pre-NDA Meeting

In addition to the previously agreed upon NDA content described above, the FDA required the following additional information to be included in the NDA submission:

- 3-month data from at least 12 to 24 newly exposed patients
- Individual patient-level data for the historical control patients, including rise time or similar timed function tests, baseline factors including steroids, and any ancillary care that affects physical function
- Dystrophin source images, and key analyses
- Study 201/202 Week 168 efficacy data

May 2015: Type C Pre-NDA Follow Up Meeting

In the May 2015 Pre-NDA meeting, FDA considered Sarepta’s proposal for the NDA to be acceptable. FDA also noted the following points:

- Data from the Study 201/202 Fourth Biopsy, taken at Week 180, while not required in the initial NDA, was also required to be submitted to the NDA post submission.
- To aid comparison of the Study 201/202 6MWT and NSAA data to historical controls, details of care such as steroid use, other medication use, physical therapy and pulmonary therapy needed to be obtained.
- Independent assessment of percent dystrophin positive fibers (PDPF) from Studies 201/202 and Study 28
- Review of available historical data regarding dystrophin expression and phenotype in BMD focusing on the natural history of Becker genotypes that would be created by skipping exon 51

Based on the FDA guidance received during the September 2014 and the May 2015 Pre-NDA meetings, the eteplirsen NDA was submitted on June 26, 2015 and filed on August 25, 2015. Priority Review status was also granted, requiring a 6-month review period compared to the standard 10-month review.

In addition, the PROMOVI (eteplirsen) confirmatory study is well underway and the ESSENCE study is due to start in the next few months. PROMOVI was designed in consultation with FDA and reflects feedback from the DMD community indicating that a placebo controlled trial of eteplirsen would not be feasible. ESSENCE was also designed in consultation with FDA as a placebo controlled confirmatory trial of PMOs for the treatment of DMD mutations amenable to exon 45 and exon 53 skipping.

Table 3: Confirmatory Studies to Support Eteplirsen Accelerated Approval

| Study | Study Design | Treatment | Duration |
|---------------------------|--|----------------------|--|
| PROMOVI (4568-301) | Open-label versus concurrent untreated control | Eteplirsen | 96 weeks |
| ESSENCE (4045-301) | Randomized, double-blind, placebo-controlled | SRP-4045 SRP-4053 | 96 weeks with planned open label extension |

October 2015 – February 2016: Key FDA Information Requests and Interactions:

Key FDA information requests and interactions following the NDA filing were as follows:

- 10 December 2015: FDA requested new functional efficacy data from the eteplirsen 201/202 studies from the Week 216 time point (approximately 4.5 years).
- 8 January 2016: Sarepta submitted 4-year functional efficacy data for the external control subjects (N=13), amenable to exon 51 skipping.
- 20 January 2016: PCNS Drugs Advisory Committee for eteplirsen (scheduled for 22 January 2016) cancelled by FDA due to a weather emergency.
- 29 January 2016: FDA requested source documents and records for the Italian DMD Telethon and Leuven Neuromuscular Research Center registries.
- 5 February 2016: The PDUFA date for the NDA was extended by 3 months to 26 May 2016. Sarepta’s submission of the additional 4-year external control data on 8 January 2016 was considered by the FDA to be a major amendment, and the delay to the NDA action date was *“to provide time for a full review of the submission.”*
- 12 February 2016: FDA requested that functional efficacy data for the upcoming Week 240 time point (approximately 5 years) of Study 201/202 be submitted for review on an expedited basis. Sarepta committed to providing the 6MWT, NSAA total score, and rise time data for review as soon as possible.
- 17-18 March, 2016: All source documents and records for the Italian DMD Telethon and Leuven Neuromuscular Research Center registries were submitted to FDA.

4. NONCLINICAL STUDIES

4.1. Exon Skipping Increases Dystrophin and Improves Function in Dystrophic Animals

The feasibility of ameliorating the DMD phenotype using exon skipping to restore the dystrophin mRNA open reading frame is supported by nonclinical research. Numerous studies in dystrophic animal models of DMD have shown that restoration of dystrophin by exon skipping leads to reliable improvements in muscle strength and function (Sharp 2011; Yokota 2009; Wu 2008; Wu 2011; Barton-Davis 1999; Goyenville 2004; Gregorevic 2006; Yue 2006; Welch 2007; Kawano 2008; Reay 2008; van Putten 2012). A compelling example of this comes from a study in which dystrophin levels following exon skipping (using a PMO) therapy were compared with muscle function in the same tissue. In dystrophic *mdx* mice, tibialis anterior (TA) muscles treated with a mouse-specific PMO maintained ~75% of their maximum force capacity after stress-inducing contractions, whereas untreated contralateral TA muscles maintained only ~25% of their maximum force capacity ($p < 0.05$) (Sharp 2011). In another study, 3 dystrophic *CXMD* dogs received at (2-5 months of age) exon-skipping therapy using a PMO-specific for their genetic mutation once a week for 5 to 7 weeks or every other week for 22 weeks. Following exon-skipping therapy, all 3 dogs demonstrated extensive, body-wide expression of dystrophin in skeletal muscle, as well as maintained or improved ambulation (15 m running test) relative to baseline. In contrast, untreated age-matched *CXMD* dogs showed a marked decrease in ambulation over the course of the study (Yokota 2009).

PMOs were shown to have more exon skipping activity at equimolar concentrations than phosphorothioates in both *mdx* mice and in the humanized DMD (hDMD) mouse model, which expresses the entire human DMD transcript (Heemskirk 2009). *In vitro* experiments using reverse transcription polymerase chain reaction (RT-PCR) and Western blot (WB) in normal human skeletal muscle cells or muscle cells from DMD patients with different mutations amenable to exon 51 skipping identified eteplirsen as a potent inducer of exon 51 skipping. Eteplirsen-induced exon 51 skipping has been confirmed *in vivo* in the hDMD mouse model (Arechavala-Gomez 2007).

4.2. Nonclinical Development of Eteplirsen

A comprehensive set of nonclinical pharmacokinetic (PK), safety pharmacology, and toxicity studies has been performed as part of eteplirsen's development.

4.2.1. Nonclinical Pharmacokinetics

Key nonclinical PK study findings include the following:

- An *in vivo* PK study in *mdx* mice demonstrated an apparent plasma half-life of approximately 6 hours, widespread distribution to skeletal, cardiac, and diaphragm muscles, high concentrations in kidneys and urine, and predominantly renal excretion

- Combined *in vitro* protein binding, cytochrome P450 enzymes (CYP) or drug transporter interactions, and hepatic microsomal metabolism study results demonstrated a low potential for drug-drug interactions for eteplirsen in humans
 - Low *in vitro* binding of ¹⁴C-eteplirsen to human plasma proteins (6.1% to 16.5%)
 - No metabolism by human hepatic microsomes
 - No *in vitro* inhibition of the major human CYP isoenzymes tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) at biologically relevant concentrations (i.e., <1 mg/mL)
 - No induction of CYP2B6 or CYP3A4 and minimal induction of CYP1A2 only at high concentrations (>1 mg/mL) in human primary hepatocyte cultures
 - No interactions as either a substrate or inhibitor of key human drug transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2, and BSEP at biologically relevant concentrations (i.e., <1 mg/mL)

4.2.2. Renal Toxicity of Eteplirsen in Animals

Good Laboratory Practice (GLP) repeat-dose toxicity studies of eteplirsen, administered by IV injection once weekly for 12 weeks in dystrophic (*mdx*) and non-dystrophic mice, for 10 weeks in juvenile rats, and for 12 and 39 weeks in non-human primates (NHPs), demonstrated that the kidney was the main target organ. Renal findings for eteplirsen in mice and NHPs consisted of non-adverse morphological changes of multifocal, renal tubular basophilia/vacuolation, with minimal-to-slight tubular degeneration. These findings were not associated with significant changes in renal-related clinical pathology parameters (e.g., serum creatinine or urea nitrogen, urine chemistries) and the no observed adverse effect level (NOAEL) was the highest dose level tested in these species (960 mg/kg in mice and 320 mg/kg in NHPs). In juvenile rats, renal histopathology findings of marked tubular dilatation, vacuolation, and basophilia were accompanied by minimal to slight necrosis, minimal hemorrhage/interstitial inflammation, increased renal weights, increased serum creatinine/urea nitrogen, and decreased creatinine clearance at the highest dose level tested (900 mg/kg) and were considered adverse. Due to the adverse renal effects at 900 mg/kg, the NOAEL in juvenile rats was 300 mg/kg. Nevertheless, renal effects of eteplirsen in animals were less severe than those reported at lower doses for the phosphorothioate antisense oligonucleotide, drisapersen (Frazier 2014). Eteplirsen plasma exposures assessed in the juvenile rat and NHP toxicity studies were high, increased in a nearly dose-dependent manner, and were 8-fold (juvenile rats) and 28-fold (NHPs) higher than human exposures, based on plasma AUC at the NOAEL versus mean human AUC at 30 mg/kg.

4.2.3. Other Nonclinical Findings for Eteplirsen

Phosphorothioates are known to cause a number of other target organ toxicities in animals, including complement activation and pro-inflammatory effects, coagulopathies, thrombocytopenia, vascular injury, and hepatic Kuppfer cell basophilia (Levin 1998; Monteith 1999; Levin 2001; Henry 2008; Frazier 2014; Engelhardt 2015; Frazier 2015). Thorough evaluations of the developing immune system in juvenile rats, which included T cell-dependent antibody responses and immunophenotyping of peripheral blood T- and B-cell subpopulations (total/helper/cytotoxic T-cells, B-cells, and NK cells), demonstrated that eteplirsen had no adverse effect on the immune

response. In addition, quantitation of the Bb, C3a, and C5a fragments of the complement alternative pathway on Day 8 and at Weeks 13 and 39 in the chronic study showed that eteplirsen did not cause complement activation at the highest dose level tested in NHPs (320 mg/kg). Injection site reactions in repeat-dose toxicity studies were infrequent, non-adverse, and showed evidence of reversibility. There was no evidence of eteplirsen-induced thrombocytopenia or vascular injury observed in mice, juvenile rats, or NHPs after repeated high weekly doses of 960 mg/kg, 900 mg/kg, or 320 mg/kg, respectively.

A safety pharmacology study in NHPs showed that single IV injections of eteplirsen at doses up to 320 mg/kg had no adverse effects on cardiovascular, respiratory, renal, hepatic, or global neurological functional assessments. In repeat-dose studies, no morphological changes were observed in the heart, no effects on electrocardiogram parameters, including heart rate (HR) and PR, RR, QT, and QTc intervals, and no effects on coagulation parameters were detected after once-weekly IV injections of eteplirsen in NHPs at doses up to 320 mg/kg for 39 weeks.

No effects were detected on the male reproductive system in mice, juvenile rats, and NHPs in repeat-dose toxicity studies. Eteplirsen did not affect neuromuscular development in juvenile rat pups, including performance in forced swim tests (Cincinnati water maze), grip strength measurements, hind-limb splay, and motor activity, after once-weekly IV injections of doses up to 900 mg/kg. This dose level produced exposures approximately 32-fold higher than human exposures based on plasma AUC. No pathological changes in skeletal muscles or histopathological evidence of hepatic Kupffer cell basophilia were observed in any of the repeat-dose toxicity studies conducted in mice, juvenile rats, or NHPs. Finally, there was no evidence of eteplirsen-associated mutations, chromosomal aberrations, or clastogenic potential in the International Conference on Harmonisation (ICH) standard battery of genotoxicity tests.

5. CLINICAL PHARMACOLOGY

The eteplirsen clinical pharmacology program is currently composed of the human pharmacodynamic and pharmacokinetic data generated from 4 clinical trials (Studies 33, 28, 201, and 202) conducted in patients with DMD. In addition, nonclinical studies conducted with human biomaterials are described in [Section 4.2.1](#).

5.1. Pharmacokinetics

Plasma and urine samples were collected from eteplirsen-treated patients for analysis of eteplirsen levels in order to estimate PK parameters in the pivotal Studies 201/202 and supportive Study 28. Overall, the PK profile of eteplirsen was predictable and demonstrated a half-life of between 3-4 hours with the majority of eteplirsen eliminated within 24 hours and no significant accumulation in plasma observed following once weekly dosing.

In Studies 201/202 (in which patients received IV eteplirsen at doses of 30 or 50 mg/kg), the PK profile of eteplirsen was consistent across the time points assessed, and there were no notable differences in C_{max} (maximum concentration), AUC (area under the concentration time curve), $t_{1/2}$, and CL at Weeks 12 and 152, indicating no accumulation ([Table 4](#)). Overall, the 30 and 50 mg/kg/week dose levels resulted in dose proportional C_{max} and AUC. Plasma clearance (CL_{PL}), V_{ss} (apparent volume of distribution at steady state), and $t_{1/2}$ (half-life) were similar at both dose levels. Results of 24-hour urine collections in eteplirsen-treated patients showed that approximately 64% of the dose was excreted as unchanged drug at the 30 mg/kg dose level and approximately 69% at the 50 mg/kg dose level.

Table 4: Plasma Pharmacokinetics at Weeks 12 and 152 in Studies 201/202

| Study 201/202 | | Mean Plasma Pharmacokinetic Parameters | | | | | | |
|---------------------|------------|--|-------------------|--------------------------------|-------------------------------|----------------------|------------------|----------------|
| Treatment Group (n) | Time Point | T_{max} (hr) | C_{max} (ng/mL) | AUC ₀₋₂₄ (hr*ng/mL) | AUC _{0-∞} (hr*ng/mL) | CL_{PL} (mL/hr/kg) | V_{ss} (mL/kg) | $t_{1/2}$ (hr) |
| 30 mg/kg (4) | Week 12 | 1.08 | 77,200 | 91,040 | 91,170 | 339 | 601 | 3.30 |
| 50 mg/kg (4) | | 1.14 | 124,600 | 180,825 | 181,162 | 319 | 638 | 3.17 |
| 30 mg/kg (6)* | Week 152 | 1.12 | 85,067 | 127,457 | 127,810 | 244 | 526 | 3.54 |
| 50 mg/kg (6)* | | 1.11 | 125,750 | 192,618 | 193,181 | 322 | 690 | 3.78 |

AUC₀₋₂₄=area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-∞}=area under the plasma concentration-time curve from time 0 to infinite time; CL_{PL} =total clearance of drug after extravascular administration; C_{max} =observed maximum plasma concentration; $t_{1/2}$ =elimination half-life; T_{max} =time to the observed maximum plasma concentration; V_{ss} =apparent volume of distribution at steady-state

* Includes 2 placebo subjects who began eteplirsen dosing at Week 25

In Study 28, in which patients received IV eteplirsen at doses of 0.5, 1, 2, 4, 10, or 20 mg/kg/wk for 12 weeks. The plasma half-life was short, ranging between 1.6 and 3.6 hours, indicating rapid elimination. At the 2 highest dose levels (10 and 20 mg/kg), renal clearance accounted for 63.8% and 60.5% of total clearance, respectively, and was approximately the same as glomerular filtration rate in healthy boys between 5 to 15 years of age ([Harriet Lane Handbook 2015](#)).

Renal clearance ranged from 116 to 229 mL/hr/kg across dose levels. In units of mL/min, renal clearance across dose levels ranged from 62.6 mL/min to 119.4 mL/min, which spans the range

of glomerular filtration rate in healthy boys age 5 to 15 (approximately 44 to 125 mL/min). This estimate was made via a commonly used pediatric glomerular filtration rate formula (Schwartz and Gauthier, 1985) along with Centers for Disease Control (CDC) growth charts from 2000 (MedCalc.com) and estimates of plasma creatinine concentration in children.

Analyses of PK characteristics in subgroups (demographic or disease characteristics) were not performed due to the uniformity of the patient populations in the clinical studies and the relatively small sample size. However, no significant differences in PK characteristics were observed in nonclinical studies between juvenile and adult rats, suggesting that eteplirsen human PK is not likely to be age dependent.

5.2. Pharmacodynamic Effects

The pharmacodynamic effects of eteplirsen administration were evaluated in patients with DMD by examination of muscle biopsy tissue samples obtained during clinical trials.

- The mechanism of action of eteplirsen is exon 51 skipping during mRNA processing, which results in the production of internally shortened dystrophin mRNA and ultimately dystrophin protein. Exon 51 skipping was confirmed by RT-PCR analysis of dystrophin mRNA extracted from muscle tissue samples following eteplirsen administration in all patients who were treated with eteplirsen.
- The molecular goal of eteplirsen therapy is induction of dystrophin production which was demonstrated by 3 complementary methods; determination of percent dystrophin positive fibers, testing for dystrophin intensity and Western Blot. Evaluation of dystrophin positive fibers not only demonstrate dystrophin production, but also correct localization of the newly formed dystrophin at the sarcolemma membrane.

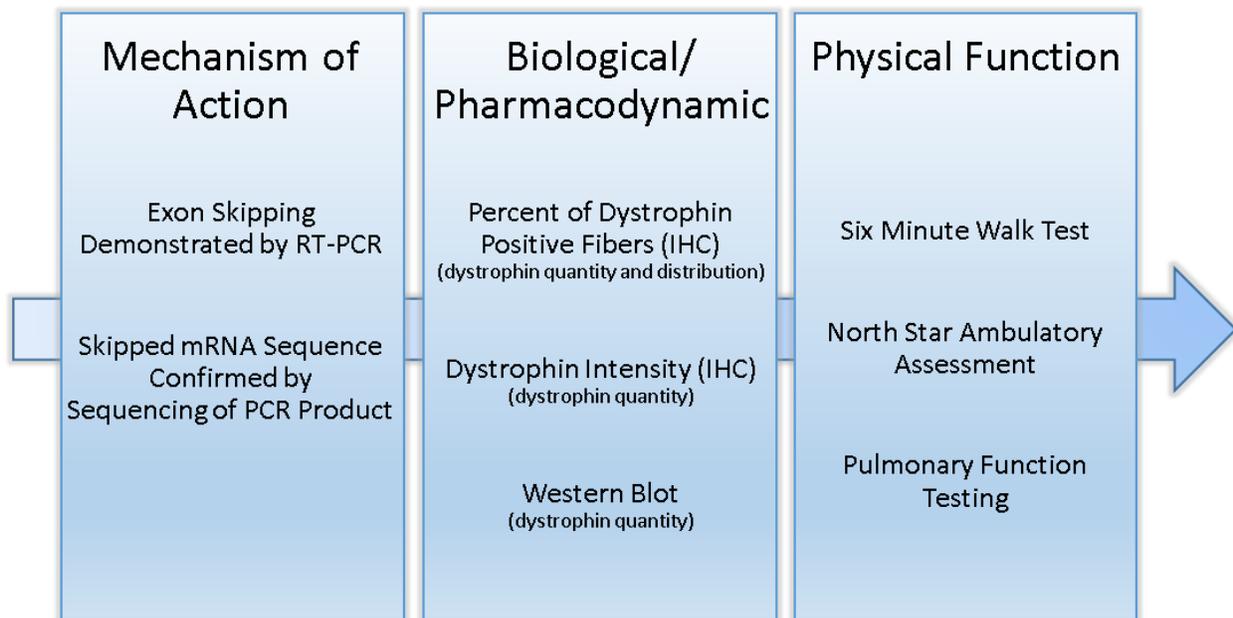
5.3. Drug-Drug Interactions

As noted in Section 4.2.1, results of *in vitro* studies indicated that eteplirsen was not metabolized by hepatic microsomes, was not a potent inducer or inhibitor of the major human CYP enzymes, and was not a substrate, nor did it have any major inhibitory potential for any of the key human drug transporters. Furthermore, published data show that corticosteroid medications used in the treatment of DMD are not expected to alter the pharmacokinetics or efficacy of exon skipping therapy (Verhaart 2012).

6. ETEPLIRSEN CLINICAL STUDIES CONTRIBUTING TO EVALUATION OF EFFICACY

Across the clinical studies the efficacy of eteplirsen has been evaluated by a continuum of study endpoints that reflect the mechanism of action, pharmacodynamics effects and clinical outcomes relevant to DMD.

6.1. Clinical Studies Contributing to Pharmacodynamic Endpoints and Clinical Efficacy



The eteplirsen clinical development program was initiated in pediatric DMD patients with a mutation amenable to exon 51 skipping who received eteplirsen intramuscularly at very low doses in Study 33 in order to demonstrate proof of principle for exon 51 skipping.

- **Proof of Concept Study 33** was the first study, conducted in boys with DMD (primarily non-ambulatory [N = 7]). A single- IM dose of either 0.09 or 0.9 mg was injected into the extensor digitorum brevis muscle of one foot with placebo injected into the other foot. RNA analyses demonstrated that eteplirsen resulted in exon 51 skipping and immunohistochemistry showed production of novel dystrophin.

After demonstrating the mechanism of action and production of dystrophin in Study 33, a dose-ranging study (Study 28) administered eteplirsen at dose levels up to 20 mg/kg.

- **Dose-Ranging Study 28** is a completed 12-week study administering 0.5 to 20 mg/kg of eteplirsen by weekly IV infusion to ambulatory pediatric DMD patients (N = 19). Exon skipping and induction of dystrophin protein expression by eteplirsen was shown with most consistent results observed for the higher dose levels of 10 and 20 mg/kg. No dose limiting toxicities were identified.

Based on demonstration of mechanism of action from these two early studies, a double-blind, placebo-controlled Phase 2 study (Study 201) was designed to evaluate clinical outcomes. Since

the maximum tolerated dose of had not been identified in Study 28, higher doses of eteplirsen, 30 and 50 mg/kg weekly IV infusion, were selected for Study 201. Study 202 was an open-label extension study evaluating eteplirsen for a period of approximately 4 years, and included assessments of 6MWT, loss of ambulation, NSAA and PFTs.

- **Pivotal Study 201 and its ongoing extension, Study 202** are conducted in ambulatory DMD boys 7 to 13 years of age (N = 12) administering 30 or 50 mg/kg by IV infusion. These studies have been ongoing for approximately 4 years with collection of clinical and biologic outcome data. No dose limiting toxicities were identified for the 30 or 50 mg/kg doses.

Overall across 4 studies there were 36 patients that contributed to the evaluation of pharmacodynamic data and 12 patients (from pivotal studies 201/201) with long term clinical outcome data. Key aspects of the 4 studies are summarized in [Table 5](#).

Table 5: Clinical Studies Contributing to Pharmacodynamic Endpoints and Clinical Efficacy

| Descriptor | Study Number | | | |
|-----------------------------|---|--|---|---|
| | Pivotal | | Supportive | |
| | Study 201 | Study 202 | Study 28 | Study 33 |
| Study Design | Randomized, double-blind, placebo-controlled, multiple-dose, single-center (US) study | Multi-center (US), open-label, multiple-dose extension study | Dose-ranging study Open-label, multiple-dose, (UK) | Proof of concept Single-blind, placebo-controlled, single-dose, investigator-sponsored, (UK) |
| Dosing Regimen | Eteplirsen 30 or 50 mg/kg/week, or placebo (IV) Weeks 1-24, then eteplirsen 30 or 50 mg/kg Weeks 25-28 | Eteplirsen 30 or 50 mg/kg/week (IV) | Eteplirsen 0.5, 1.0, 2.0, 4.0, 10.0 or 20.0 mg/kg/week (IV) | Eteplirsen 0.09 or 0.9 mg IM in the EDB of 1 foot and placebo (IM) in the EDB of the opposite foot |
| Endpoints | Primary = Change from BL in PDPF at Week 12 (50 mg/kg group) and at Week 24 (30 mg/kg group). Other = 6MWT, LOA, NSAA, rise time and PFTs; Exon skipping (RT-PCR) and dystrophin PDPF and intensity in biopsied muscle | Primary Functional = Change from BL in 6MWT at Week 48 Primary Biological = Change from BL (of Study 201) to Week 48 in PDPF Other = Exon skipping (RT-PCR) and change from BL in dystrophin intensity, LOA, NSAA, rise time and PFTs | Primary = safety and tolerability Exploratory = Change from BL to Week 14 in dystrophin PDPF Other = Change from BL to Week 14 in dystrophin intensity and protein levels (Western blot) | Primary = safety Key Secondary = Exon Skipping (RT-PCR); Restoration of dystrophin protein expression and the DAPC |
| Required Age at Entry (yrs) | 7-13 | | 5-15 | 10-17 |
| Study Status | Completed | Ongoing | Completed | Completed |
| No. Enrolled | 12 | | 19 | 7 |
| No. Completed | 12 | NA | 18 | 7 |
| Study Period | July 2011 – Feb 2012 | Feb 2012 – Nov 2015 for Efficacy | Jan 2009 – June 2010 | Oct 2007 – April 2009 |
| Study Duration | 28 Weeks | Year 4 | 12 Weeks | Single Dose |

Abbreviations: BL=Baseline; yrs=years; EDB=extensor digitorum brevis muscle; IM=intramuscular; IV=intravenous; No.=number; LOA=Loss of Ambulation; NSAA=North Star Ambulatory Assessment; PDPF=percent dystrophin positive fibers; PFT=pulmonary function testing; RT-PCR=reverse transcriptase-polymerase chain reaction; US=United States; UK=United Kingdom; Wk=week.

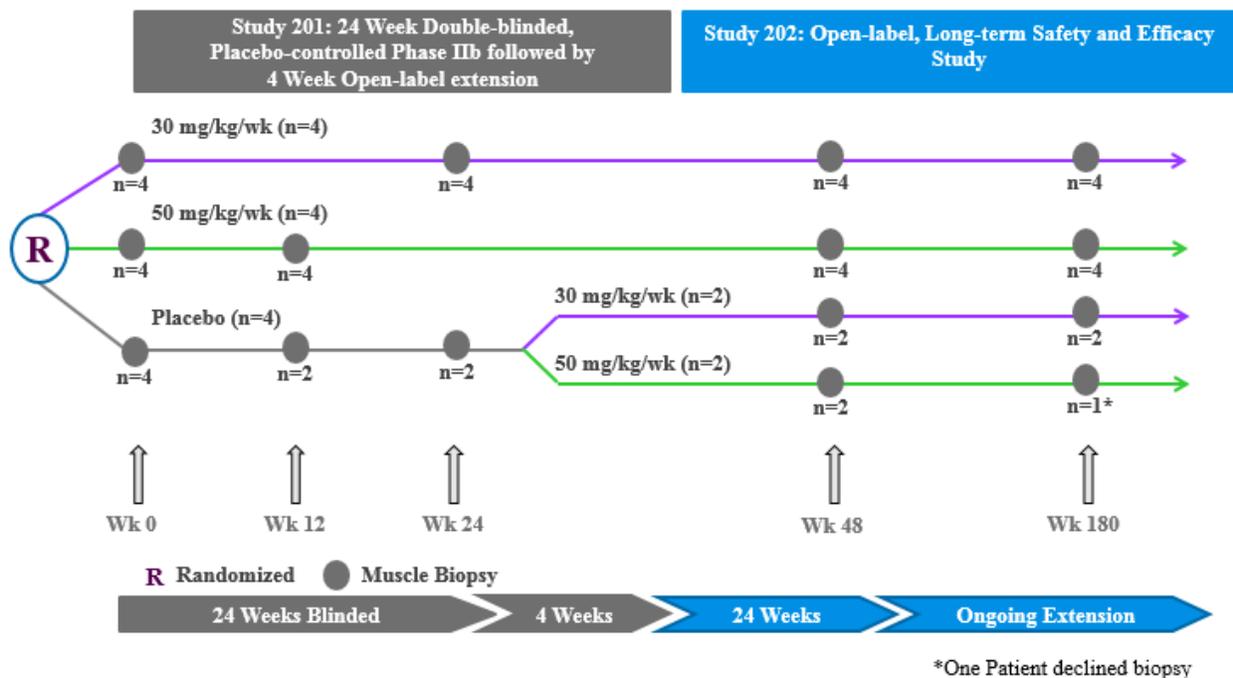
6.2. Pivotal Studies 201/202

6.2.1. Study Design

Study 201 is a completed, 28-week double-blind, placebo-controlled study of eteplirsen in 12 ambulatory boys with DMD mutations amenable to exon 51 skipping. Eligible patients were randomized to receive weekly IV infusions of 30 (N = 4) or 50 mg/kg eteplirsen (N = 4) or placebo (N = 4) for the first 24 weeks. Afterwards, the 4 patients originally randomized to placebo, rolled over to open label eteplirsen of 30 mg/kg (N = 2) or 50 mg/kg (N = 2). Figure 14 presents a schematic for Studies 201/202.

- Following completion of Study 201, all 12 patients continued receiving weekly eteplirsen in the ongoing extension Study 202 for approximately 4 years.
- During both studies, muscle biopsies of upper arms were obtained for assessment of exon skipping and dystrophin production for all patients at Baseline and study Weeks 48, and 180. In order to minimize the overall number of muscle biopsies, half of the study patients also underwent biopsies at Week 12 (50 mg/kg) and the other half of patients had an additional muscle biopsy at Week 24 (30 mg/kg).
- Clinical outcomes of 6MWT, LOA, NSAA, rise time, pulmonary function tests and other functional measures were performed to assess changes in muscle function over time and have been collected through Year 4 for the 12 patients enrolled in Study 201/202.

Figure 14: Schematic of Study Flow for Pivotal Studies 201/202



6.2.2. Inclusion and Exclusion Criteria

Study 201 inclusion and exclusion criteria were designed to select a homogeneous population of DMD boys that would be expected to experience a predictable decline in 6MWT over the course of the study. Selection of this narrow population was considered the best group to evaluate whether stabilization of function would occur with eteplirsen intervention. Accordingly, the inclusion criteria specified boys aged 7 to 13 with baseline 6MWT between 180 and 440 meters. The age of 7 years was selected as this was the time-point in the course of DMD when progressive muscle degeneration and loss of function begin to outpace natural growth and maturation such that DMD patients functionally decline. The impact of age and baseline 6MWT on performance on 6MWT are described in the current DMD literature ([Henricson 2013a](#); [Pane 2014a](#); [McDonald 2010b](#); [Mazzone 2013](#); [Ricotti 2013](#); [Ricotti 2015](#)).

Steroid use may also influence performance on the 6MWT; ([Pane 2014a](#); [Henricson 2013a](#); [McDonald 2010b](#); [McDonald 2013b](#); [Ricotti 2013](#); [Ricotti 2015](#)). DMD clinical trial design guidelines, recommend selection of a population of patients having similar anticipated disease trajectories. ([FDA 2015b](#)) Therefore, Study 201 required that patients received a stable dose of steroids for ≥ 24 weeks prior to enrollment. Study 201 Key Inclusion criteria are provided in [Table 6](#). [Appendix 2](#) provides a complete list of Study 201 inclusion and exclusion criteria.

Table 6: Key Entry Criteria for Pivotal Study 201

| | |
|--------------------------------|--|
| Population | Male with DMD |
| | Genetically confirmed deletion mutation amenable to exon 51 skipping |
| | Aged 7-13 years |
| | Intact L/R biceps or alternative upper arm muscle group |
| Disease characteristics | Ambulatory with baseline 6MWT 180-440 meters |
| | Stable cardiac function with LVEF >40% on screening echocardiogram |
| | Stable pulmonary function with FVC $\geq 50\%$ predicted; supplemental oxygen not required |
| | Stable dose of oral corticosteroids ≥ 24 weeks before study |
| | No cognitive or behavioral disorder that would impair ability to perform on 6MWT |

6.2.3. Study 201/202 Pre-specified Endpoint Results

6.2.3.1. Primary Endpoint of Study 201

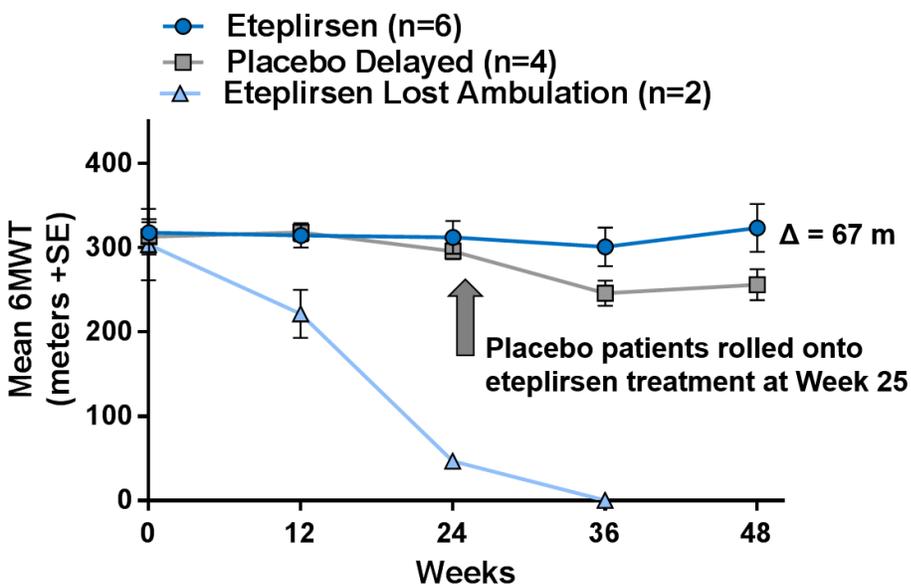
The primary endpoint of Study 201 was dystrophin production at Weeks 12 and 24. Although no significant dystrophin increase was observed at 12 weeks for the 50 mg/kg cohort, the endpoint was achieved at Week 24 for the 30 mg/kg dose group. At 24 weeks the 30 mg/kg dose group demonstrated a significant increase of dystrophin in comparison to both baseline pre-treatment values and a significant increase of dystrophin relative to placebo treated patients. These findings suggest that duration of 24 weeks of eteplirsen therapy is required for significant dystrophin production.

6.2.3.2. Primary Endpoint of Study 202

The primary functional endpoint of Study 202 was comparison of Week 48 6MWT results for boys originally randomized to eteplirsen vs placebo. A co-primary endpoint was dystrophin production at Week 48.

In the analysis of Week 48 6MWT there was no difference between eteplirsen treated and placebo patients. This was possibly due to the fact that 2 boys with the lowest 6MWT values at baseline (patients 009, 010) were randomized to eteplirsen and experienced rapid decline of 6MWT in the first 24 weeks, followed by loss of ambulation. In retrospect, after understanding that it takes 24 weeks for significant dystrophin production, eteplirsen treatment may have been introduced too late in the course of their disease. An exploratory analysis of the 6MWT removing these two boys with early loss of ambulation showed relative stability across the remaining eteplirsen-treated boys. In addition, compared to the boys originally randomized to placebo, those on eteplirsen showed a mean difference of 67 meters at the end of 48 weeks. See Figure 15.

Figure 15: Study 201/202: Exploratory Analysis of 6MWT for Eteplirsen vs. Placebo (excluding 2 eteplirsen-treated boys with ambulatory decline prior to significant dystrophin production)



Based on these encouraging but limited results, the hypothesis of eteplirsen efficacy was strengthened and it was decided that Study 202 be further extended to continue observation and collection of longitudinal clinical outcomes.

The basis of the eteplirsen NDA application is the analysis of the clinical outcomes from Studies 201/202 compared to external control cohort derived from external DMD registries.

6.3. External Control Cohort Used For Comparison of Long Term Efficacy Data

6.3.1. Selection of External Registries for Long Term Clinical Outcome Data

Given the relatively short duration of 24 weeks for the placebo-controlled portion of Study 201, there was an absence of long-term concurrent placebo controlled data for comparison of clinical efficacy of eteplirsen. Therefore as recommended by the FDA, Sarepta sought to identify appropriate external observational registries with longitudinal clinical outcome data.

The selection process for external registries, as well as identification of individual patients for the external control cohorts was conducted in a manner to minimize the potential for selection bias. The clinical outcome experience from the external cohorts was used for comparison of 6MWT, LOA, NSAA and ability to rise from supine independently.

Sarepta consulted with external DMD experts and reviewed findings from international DMD groups (International DMD Working Group 2011, Collaborative Trajectory Analysis Project) to identify potential registries that could provide individual patient 6MWT data including at least a baseline and post-baseline value for 6MWT. Twelve candidate external DMD registries with clinical outcome data were identified; however, only 2 databases had available, prospectively collected, 6MWT data including a baseline and at least 1 post-baseline value:

- Italian Telethon DMD Registry database (N = 97); Professor Eugenio Mercuri, MD, PhD (Catholic University in Rome); 11 participating tertiary care centers
- Leuven Neuromuscular Reference Center (NMRC) database (N = 89); Professor Nathalie Goemans, MD (University Hospitals in Leuven, Belgium); single site

6.3.2. Registry Characteristics Similar to Eteplirsen Studies 201/202

Although the two registries were chosen primarily based on availability of 6MWT outcomes, both registries had characteristics including entry criteria and DMD standards of care comparable to Study 201/202. These registries included the requirement for a genetically confirmed diagnosis of DMD, followed patients over comparable time period, and excluded patients with known cognitive or behavioral disorders that would be likely to impair compliance with the functional assessments. These registry characteristics are outlined in [Table 7](#).

In addition, as with Studies 201/202, both registries follow international DMD patient care guidelines ([Bushby 2010a](#); [Bushby 2010b](#)) used to set standards for the use of steroids as well as the use of physical therapy and orthotic devices to support continued ambulation.

- While guidelines were published in 2010, clinics in both registries had been adhering to the standards at the time the registry studies were initiated including the use of steroids.
- The 2 lead physical therapists for the Italian Telethon Registry and Studies 201/202 were part of an international group which trained physical therapists on the 6MWT, further ensuring consistency and standardization of collection of 6MWT data.

Table 7: External DMD Registry Characteristics Compared to Studies 201/202

| | External DMD Registries | Studies 201/202 |
|---|--|--|
| Genetically confirmed diagnosis of DMD | Required | Required |
| Patients with known cognitive or behavioral disorders that would impair compliance with functional assessment | Excluded | Excluded |
| Inclusion of patients meeting registry or study criteria | All patients included | All patients included |
| Time period for evaluation and data collection follow-up of patients | Leuven NMRC (2007 – present), Italian Telethon (2008 – present) | 2011 – present |
| Standard of care for use of steroids | International DMD guidelines (Bushby 2010a ; Bushby 2010b) | International DMD guidelines (Bushby 2010a ; Bushby 2010b) |
| Use of physical therapy and orthotic devices to support continued ambulation | Italian Telethon investigators, as well as the principal investigator of the Leuven NMRC, are members of TREAT-NMD, a European organization of neuromuscular experts that promote the use of these international treatment guidelines for DMD. | Followed international DMD guidelines for use of physical therapy and orthotic devices. |
| 6MWT assessment method | ATS procedure for 6MWT including assessor training and encouragement script | ATS procedure for 6MWT including assessor training and encouragement script |

6.3.3. Criteria for Identification of Patients for External Control Cohort was Based on Study 201 Inclusion Criteria

The two external registries (Leuven NMRC and Italian Telethon) provided Sarepta with a combined data set of 186 patients. Individuals were identified for inclusion in the external control group(s) using the key prognostic entry criteria for Study 201. Of note, all patients who met these criteria were included in the external control groups:

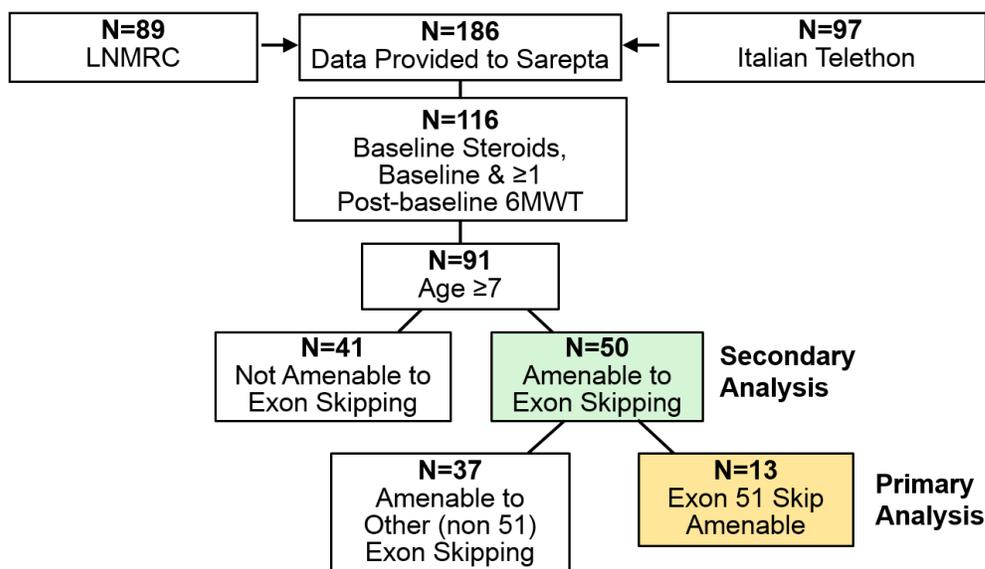
- They were required to be ≥ 7 years of age,
- Ambulatory with baseline 6MWT and at least 1 post baseline 6MWT result
- Receiving glucocorticoid therapy per treatment guidelines
- Genetically confirmed DMD (all patients)
 - Amenable to exon 51 skipping therapy (primary external control group)
 - Amenable to any exon skipping therapy (secondary external control group)

6.3.4. Schematic for Identification of External Control Groups

This schematic illustrates the application of the selection filters used to identify external control patients.

- From the total 186 untreated DMD patients included in the registries, 116 received glucocorticoids at baseline and had baseline 6MWT and at least one post-baseline 6MWT results.
- 91 of the 116 patients were ≥ 7 years of age
- 50 of the 91 patients had DMD genetic mutations amenable to any exon skipping therapy
- 13 of the 50 patients had DMD mutations specifically amenable to exon 51 skipping therapy

Figure 16: Identification External Control Groups for 6MWT Comparison



Thus, 2 external control groups were identified for comparative analysis to eteplirsen-treated patients:

- **External control group amenable to exon 51 skipping (N = 13) Primary Analysis**
This is the most relevant comparator for the 4-year 6MWT data from Study 201/202 eteplirsen-treated patients. A subset of 10 external control patients from the Italian Telethon registry had 3-year NSAA data; NSAA data were not provided for patients in the Leuven NMRC.
- **External control group amenable to any exon skipping (N = 50) Secondary Analysis**
This secondary group provided a larger sized group for comparison of the 6MWT data for 3 years, albeit in a population of DMD with a mutation amenable to any kind of exon skipping. The secondary group also included 8 patients with DMD mutations amenable to skipping exon 44, which typically have a milder disease course.

6.4. Comparability of Baseline Characteristics of Eteplirsen Treated Patients and the External Control Groups

Analysis of key baseline characteristics for the 12 patients treated with eteplirsen in the pivotal 201/202 studies and the primary (exon 51 skipping, N = 13) and secondary (any exon skipping, N = 50) external control groups used for comparison on the 6MWT are presented in [Table 8](#).

Study 201/202 patients had a mean of 9.41 years of age at baseline, while patients in the primary (N = 13) and secondary (N = 50) external control groups had mean ages of 9.45 and 9.68, respectively. Genetic mutations were similar between Studies 201/202 and those in the primary external group (N = 13), with each specific type of genetic mutation observed in Study 201/202 also represented among the boys in the primary external control cohort. Mean 6MWT scores across the eteplirsen treated and external control groups were within 10 meters of each other and the distribution of patients over the range of baseline scores for both 6MWT and NSAA was similar ([Figure 17](#)).

Importantly, all patients in all groups had been on steroids for at least 6 months prior to baseline and remained on steroids throughout the study or follow-up period.

The high comparability of the treated pivotal study and untreated control patients across these key baseline parameters confirms the validity of the process used for selection of the external controls. Baseline characteristics for the individual patients in Study 201/202 (N = 12) as well as the external control of exon 51 skippable (N = 13) are provided in [Appendix 2](#).

Table 8: Key Baseline Characteristics of Eteplirsen Patients in Studies 201/202 vs External Controls

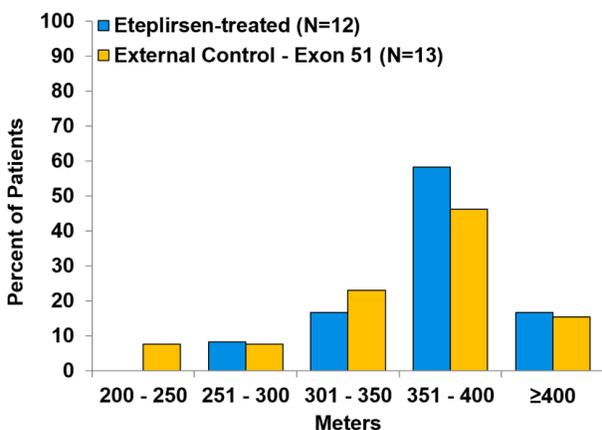
| Parameter | Pivotal Study | Untreated External Control Groups | |
|------------------------------|---------------------------|--|---|
| | Study 201/202 (N = 12) | Primary Analysis Exon 51 Skipping (N = 13) | Secondary Analysis Any Exon Skipping (N = 50) |
| Male Gender | 100% | 100% | 100% |
| Age, years | N = 12 | N = 13 | N = 50 |
| Mean (SD) | 9.41 (1.18) | 9.45 (1.45) | 9.68 (1.52) |
| Median | 9.7 | 9.0 | 9.54 |
| Min, Max | 7.3, 11 | 7.3, 11.8 | 7.0, 13.0 |
| 6MWT Distance (m) | N = 12 | N = 13 | N = 50 |
| Mean (SD) | 363.2 (42.19) | 357.6 (66.75) | 355.7 (87.28) |
| Median | 370 | 373 | 356 |
| Min, Max | 256, 416 | 200, 458 | 100, 558 |
| Genotype (exon 51 skippable) | N = 12 | N = 13 | Amenable to any exon skipping ^a |
| 45-50 | 3 | 3 | |
| 48-50 | 1 | 2 | |
| 49-50 | 5 | 3 | |
| 50 | 1 | 2 | |
| 52 | 2 | 3 | |
| Total NSAA Score | N = 12 | N = 10 | N = 34 |
| Mean (SD) | 24.9 (4.93) | 22.0 (6.27) | 22.7 (6.31) |
| Min, Max | 17,31 | 10,31 | 10, 32 |
| Rise Time ^d | N = 12 | N = 11 | N = 33 |
| Mean (SD) | 8.2 (7.57) | 9.6 (10.25) | 9.7 (9.36) |
| Median | 5.5 | 5.7 | 5.7 |
| Min, Max | 3.1, 30 | 2.4, 30 | 2, 30 |

Abbreviations: 6MWT = Six minute walk test; EC = external control; SD = standard deviation.

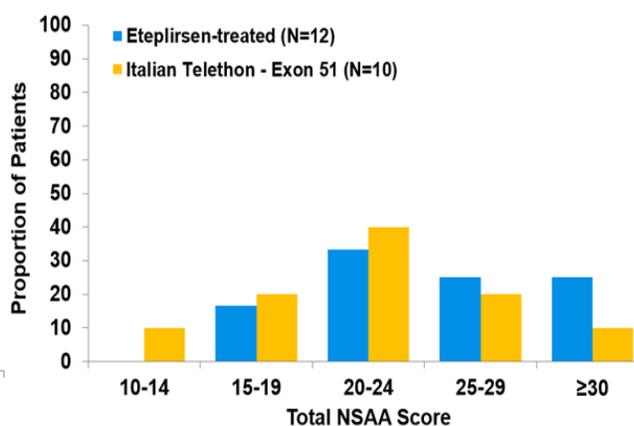
^a Eight of the 50 (16%) had deletion mutations amenable to exon 44 skipping; this genotype may have a milder phenotype compared to other skippable mutations ([Pane 2014a](#)).

Figure 17: Baseline Distribution of 6MWT and NSAA Scores for Eteplirsen-Treated Patients in 201/202 vs External Controls

A) Baseline 6 Minute Walk Test



B) Baseline NSAA



6.4.1. Comparability of Glucocorticoid Use for Eteplirsen-Treated and External Control Group (N = 13)

Patients from both Study 201/202 and the external control group received glucocorticoids for a period of at least 24 weeks prior to baseline and throughout the duration of study. The comparison of age of steroid initiation, type of steroid administered as well as schedule of regimen is provided in [Table 9](#). Details regarding the type of glucocorticoid therapy for individual patients are provided in [Appendix 3](#).

Table 9: Comparison of Glucocorticoid Use at Baseline

| | Eteplirsen Study 201/202 N=12 | External Control: Exon 51 Skip Amenable N=13 |
|------------------------------------|--|---|
| Age at steroid start, years | | |
| Mean (SD) | 5.2 (1.09) | 6.4 (2.19) |
| Median | 5.5 | 6.0 |
| Min, Max | 3.5, 6.6 | 3.1, 10.7 |
| Deflazacort | 8 (67%) | 9 (69%) |
| Prednisone | 4 (33%) | 4 (31%) |
| ≥90% recommended dose | 2 (17%) | 9 (69%) |
| Continuous | 11 (92%) | 8 (62%) |
| Intermittent | 1 (8%) | 5 (38%) |

The median age of steroid initiation was 5.5 and 6.0 years, respectively for the eteplirsen and the external control group amenable to exon 51 skipping (N = 13). The two most commonly prescribed steroids in DMD, deflazacort and prednisone, were used in equal proportion by both groups. In an analysis evaluating the percent recommended dose established by the CDC/TREAT-NMD care standards, the external control group had higher compliance with treatment guidelines compared to eteplirsen-treated patients, with 69% of external control vs only 17% of eteplirsen treatment boys receiving $\geq 90\%$ of the recommended dose (0.9 mg/kg/day deflazacort or 0.75 mg/kg/day prednisone).

Glucocorticoids in DMD may be administered on a daily schedule (continuous) or on an alternating schedule ([Bushby 2010a](#)). In the external control group (N = 13), a higher percentage of patients received an intermittent steroid regimen at baseline in comparison to eteplirsen boys (38% vs. 8%). However, in a sensitivity analysis of 6MWT including a covariate of continuous vs intermittent steroid treatment schedule, the difference in 6MWT at Year 4 was 155 meters (p=0.0023), demonstrating consistency in the favorable benefit of eteplirsen.

6.4.2. Physical Therapy and Use of Orthotic Devices Eteplirsen-Treated (N = 12) vs External Control (N = 13)

Proper physical therapy and use of orthotic devices, consistent with standard of care ([Bushby 2010b](#)) support continued ambulatory function in DMD. According to FDA guidance ([FDA 2015b](#)), comparable type and intensity of supportive care between treated and external control groups are key for the comparison to be persuasive.

Comparison of eteplirsen-treated patients and the patients from the external control group, demonstrated that most patients received regular physical therapy and showed high compliance rates with the use of orthoses to maintain lower extremity flexibility.

Most eteplirsen-treated patients as well as those in the external control group followed home stretching routines. All patients in the external control group met with a trained physical therapist at least twice a week, whereas only 5/12 eteplirsen treated boys had visits with a physical therapist at least twice a week.

In order to maintain ankle flexibility, which is important to ambulation, many boys with DMD wear night splints. The majority of patients in both cohorts wear night splints or, in the case of 2 patients in the external control cohort, were found not to need them. Details regarding comparison of physical therapy and orthoses are provided by [Table 10](#).

Table 10: Comparison of Physical Therapy and Use of Orthoses

| | | Study 201/202 Eteplirsen N = 12 | External Control N = 13 |
|--|-------------------------------|--|------------------------------------|
| Physical Therapy | PT Regimen | # of Patients | # of Patients |
| Home therapy* | Stretching with parents/other | 8 | 6 |
| Swimming* | 1 day/week | 1 | 5 |
| | 2-3 days week | 1 | 0 |
| Visits with trained physical therapist | 4-6 days/week | 2 | 5 |
| | 2-3 days/week | 3 | 8 |
| | 1 day/week | 4 | 0 |
| | 1 day/year | 1 | 0 |
| | None | 2 | 0 |
| Use of night splints (orthoses) | Use orthoses | 11 | 11 |
| | Orthoses not needed (TA<10°) | 0 | 2 |
| | Orthoses not used | 1 | 0 |

*No information regarding home therapy or swimming provided from LNMRC site

6.5. Approaches or Analyses to Address Potential Limitations of Use of an External Control Group Per ICH E10

Study 201/202 had only 24 weeks of randomized placebo-controlled data, and as such use of external control cohorts was necessary in order to compare long-term clinical outcome data. Sarepta recognizes the potential limitations (ICH E10) of using external control groups. The approach to identification of the external control groups was conducted in a manner to minimize these potential limitations. [Table 11](#) summarizes the potential issues associated with the use of an external control cohort and approaches that Sarepta used in order to address or evaluate the potential for bias.

Table 11: Approaches or Analyses to Address Potential limitations of Use of an External Control Group Per ICH E10*

| Issue | Approach to Address Limitation | Relevant Section in Briefing Document |
|---|---|---------------------------------------|
| Inability to control bias in selection of external control | Selected all registries with available baseline and post-baseline 6MWT data, without regard to 6MWT results | Section 6.3.1 |
| An external control group is often identified retrospectively leading to potential selection bias | Although retrospective, all patients meeting selection criteria (based on Study 201/202 inclusion criteria) were included in the external control groups | Section 6.3.3 |
| Difficulty in establishing comparability of eteplirsen and external control groups | High degree of comparability between eteplirsen and EC on key prognostic baseline characteristics was established | Section 6.4 |
| | High compliance with DMD standard of care guidelines for glucocorticoid, physical therapy and orthotic device use | Section 6.4 |
| | Sensitivity analyses of the 6MWT with covariates of baseline 6MWT, age and glucocorticoid use confirmed the robustness of the 6MWT benefit for eteplirsen | Section 6.6.1.2 |
| Historical control groups have worse outcomes than apparently similar control group in a randomized study | The EC groups had similar or slightly better 6MWT performance compared to the placebo arm of a published randomized clinical trial (drisapersen) | Section 6.6.1.4 |
| | The EC groups experienced loss of ambulation at an age comparable to published DMD literature | Section 6.6.2.2 |

* Choice of Control Group and Related Issues in Clinical Trials

6.6. Clinical Endpoints

6.6.1. Six-Minute Walk Test (6MWT)

Given the importance of ambulatory compromise to the DMD disease process, 6MWT was chosen as the primary endpoint. The 6MWT is an integrated assessment of global muscle function and endurance that also incorporates cardiac and respiratory functions ([ATS 2002](#)) and has been established as accurate, reproducible, simple to administer, and well tolerated in ambulatory patients with DMD ([McDonald 2010a](#)). It is also clinically relevant in DMD as decline in ambulatory capacity, is associated with reductions in DMD patient- and caregiver-reported quality of life ([Bendixen 2012](#); [Bendixen 2014](#); [Magliano 2014](#); [Uzark 2012](#); [Henricson 2013b](#)). Furthermore the 6MWT is an accepted outcome measure for DMD according to the recent FDA draft guidance for industry on developing drugs for DMD ([FDA 2015b](#)).

In both the eteplirsen-treated and external control patients, the 6MWT was performed according to published methods modified for DMD patients ([ATS 2002](#); [McDonald 2010a](#)) where patients are asked to walk a pre-set course for 6 minutes during which they receive scripted encouragement and are followed by a member of the testing staff to ensure patient safety. Furthermore, both lead physical therapists for the eteplirsen study 201/202 and the Italian Telethon have collaborated in an international initiative to train physical therapists on administration of the 6MWT in DMD.

6MWT data for eteplirsen-treated and 2 groups of external control patients (primary exon 51 skipping N = 13 and secondary any exon skipping N = 50) were compared, using the analysis of covariance (ANCOVA) model with group (e.g., treatment [eteplirsen vs. untreated]) as a fixed-effect term and baseline 6MWT as a covariate. Change from baseline to Years 1, 2, 3 was summarized for both external control groups and change from baseline to Year 4 was also conducted for the external control group amenable to exon 51 skipping (N = 13).

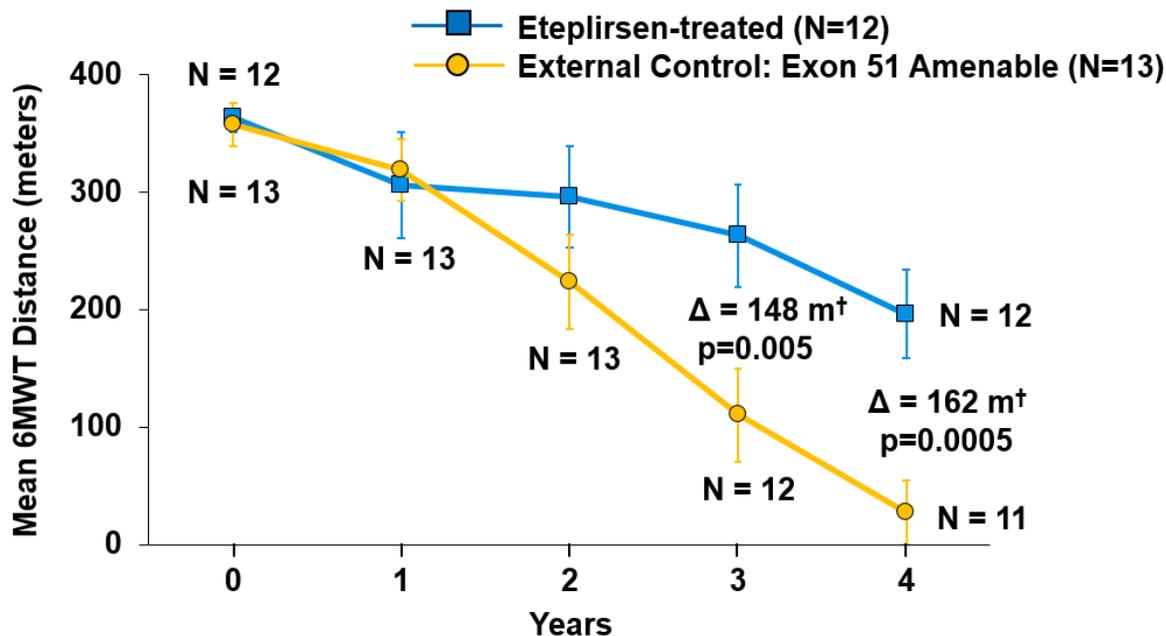
No adjustments were made for multiple comparisons as these analyses were descriptive; p-values, when provided, are nominal and included for guidance purposes only. For eteplirsen-treated patients (N = 12), data for the 30 and 50 mg/kg cohorts (N = 8) were pooled along with data for the placebo-to-eteplirsen cohort (N = 4) after correcting for the 24-week placebo-period (i.e., by counting Week 24 from study 201, the last week prior to receiving eteplirsen, as baseline).

6.6.1.1. Results for 6MWT of Eteplirsen (N = 12) vs External Control Amenable to Exon 51 (N = 13)

Eteplirsen treated patients (N = 12) showed a slower rate of decline in the 6MWT, compared to primary external controls with DMD mutations amenable to exon 51 skipping (N = 13). The 2 patient groups had similar baseline and disease progression trajectories through Year 1 supporting the comparability of the groups at baseline and during initial stages of treatment with eteplirsen. This is also consistent with pharmacodynamic data that indicates it may take up to 24 weeks to establish significant dystrophin production. As the study progresses, the stabilization of ambulation in eteplirsen-treated patients is juxtaposed against the predictable decline of ambulation in untreated external controls, the impact of eteplirsen becomes apparent.

After Year 1 the treated and untreated patients began to diverge, resulting in a 67-meter difference in 6MWT decline by Year 2, and a larger significant ($p=0.0052$) difference of 148 meters between the groups by Year 3 and 162 meters by Year 4 ($p=0.0005$) (Figure 18). Of note, all 10 of the eteplirsen boys who were ambulant at the time of NDA submission remain able to walk at Year 4; their ages range from 11.0 years to 14.6 years, with 4 of the boys aged 14 or older. For the external control group on the other hand, except for two boys with missing data, and one ambulatory boy, the remaining 10 boys had lost ambulation by Year 4.

Figure 18: Mean 6MWT Values Over Time in Eteplirsen-Treated Patients (Studies 201/202) vs. Primary External Controls



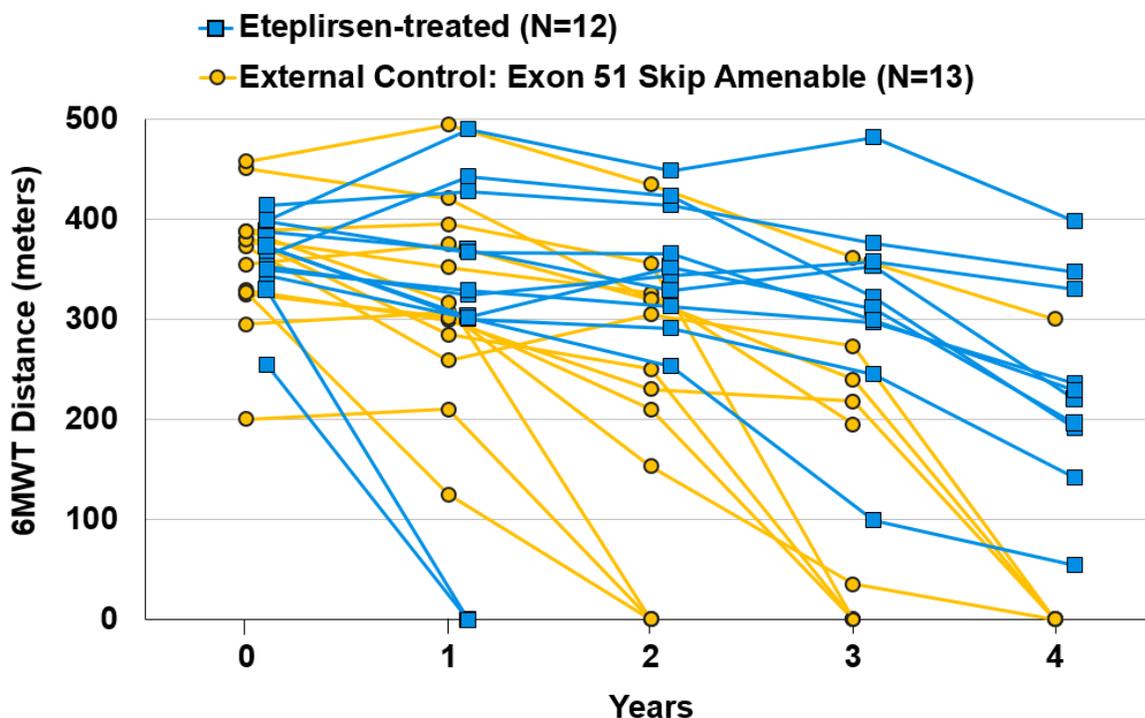
† Difference in mean change from baseline
 Patients who lost ambulation contributed a score of 0 to the mean
 1 EC Subject was missing data at Year 3 & 4, 1 EC Subject was missing data at Year 4 only

Table 12: Mean 6MWT Values at Baseline Through Year 4

| | Baseline | Year 1 | Year 2 | Year 3 | Year 4 |
|----------------------------|---------------|----------------|----------------|----------------|----------------|
| Eteplirsen, n | 12 | 12 | 12 | 12 | 12 |
| Mean (SD) | 363.2 (42.19) | 305.8 (155.32) | 295.9 (148.98) | 263.1 (151.74) | 196.3 (130.22) |
| External Control, n | 13 | 13 | 13 | 12 | 11 |
| Mean (SD) | 357.6 (66.75) | 318.6 (94.20) | 223.5 (145.43) | 110.3 (136.21) | 27.3 (90.45) |

In the analysis of individual 6MWT values over time, 2 of the eteplirsen-treated patients (blue lines) lost ambulation by Year 1. The eteplirsen patients (twin brothers, Patients 009 and 010) had the lowest 6MWT scores at baseline, hence they may have been at greater risk for loss of ambulation prior to initiation of treatment. All boys from either the eteplirsen Study 201/202 or the external control cohort who lost ambulation, continued to be included in the overall analysis of 6MWT contributing a value of “0” meters to the mean (Figure 19). A list of individual 6MWT results for both Study 201/202 patients (N = 12) as well as the external control cohort amenable to exon 51 skipping (N = 13) is provided in Appendix 7.

Figure 19: Individual 6MWT Values Over Time in Eteplirsen-Treated Patients (Studies 201/202) vs. External Control (N = 13)



6.6.1.2. Sensitivity Analyses of the Primary Functional Efficacy Endpoint: 6MWT

Sensitivity analyses were performed on the Year 4 6MWT change from baseline data to evaluate the robustness and validity of the primary efficacy analysis. A series of sensitivity analyses evaluated the potential for bias based on variation in key baseline prognostic factors such as age and 6MWT.

Additional analyses evaluated the potential for bias caused by violations of normality assumptions, bias caused by missing data, or bias caused by imbalance in other characteristics such as glucocorticoid use, baseline rise time, height, and weight. As summarized below and in [Table 13](#) for every sensitivity analysis performed, the difference between the eteplirsen-treated and untreated external controls in the change from Baseline on the 6MWT remained clinically meaningful with nominally significant p-values. Details for the methodologies of these analyses are provided in [Appendix 8](#).

Table 13: Sensitivity Analyses for 6MWT in Eteplirsen-Treated (N = 12) vs. External Control Amenable to Exon 51 Skipping (N = 13)

| Potential Issue Addressed | Row | Comparison: Change from Baseline in 6MWT in Eteplirsen-Treated (N = 12) vs. Untreated External Control (N = 13) | LS Mean Difference (meters) | P-Value |
|--|-----|---|-----------------------------|---------|
| Bias Caused by Imbalance in Important Baseline Prognostic Factors | 1 | ANCOVA Covariates: Baseline 6MWT, Age | 163 | 0.0009 |
| | 2 | ANCOVA Covariates: Baseline 6MWT, Steroid Schedule (Intermittent vs Continuous) | 155 | 0.0023 |
| | 3 | ANCOVA Covariates: Baseline 6MWT, Age, Age at Start of Steroids | 158 | 0.0040 |
| Bias Caused by Violation of Normality Assumption | 4 | ANCOVA with Baseline 6MWT as a covariate, rank transformation as the outcome for 6MWT | NA ^a | 0.0009 |
| | 5 | ANCOVA with Baseline 6MWT and age as covariates, rank transformation as the outcome for 6MWT | NA ^a | 0.0010 |
| Bias Caused By Missing Data | 6 | MMRM Covariates: Baseline 6MWT, age | 151 | 0.0007 |
| | 7 | MMRM analysis with Baseline 6MWT and age as covariates and rank transformation as the outcome for 6MWT | NA ^a | 0.0037 |
| | 8 | ANCOVA Covariate: Baseline 6MWT LOCF for missing data | 135 | 0.0039 |
| | 9 | ANCOVA Covariates: Baseline 6MWT, age LOCF for missing data | 135 | 0.0047 |
| Bias Caused by Imbalance in Other Characteristics (Baseline Rise Time, Height, and Weight) | 10 | ANCOVA Excluding 1 subject without Rise Time Covariate: Baseline 6MWT | 155 | 0.0017 |
| | 11 | ANCOVA Excluding 1 subject without Rise Time Covariates: Baseline 6MWT, Baseline Rise time | 173 | 0.0009 |
| | 12 | ANCOVA Covariates: Baseline 6MWT, Age, Height | 122 | 0.0225 |

Abbreviations: 6MWT = 6 Minute Walk Test; ANCOVA = analysis of covariance; LS = least squares; LOCF = last observation carried forward; MMRM = Mixed Model Repeated Measures; NA = not applicable.

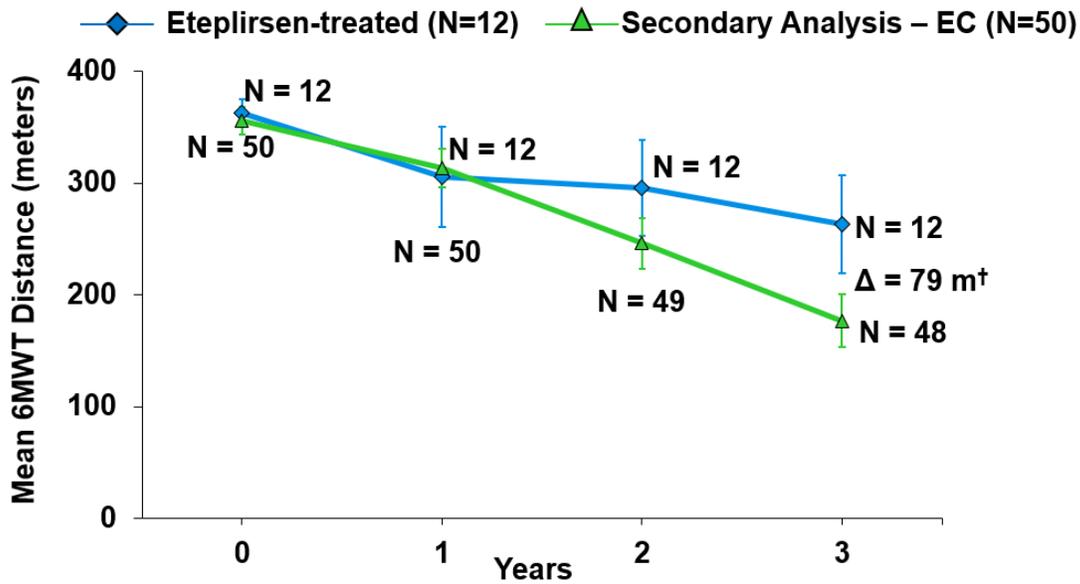
^a Not applicable as the data being analysed are rank-transformed.

6.6.1.3. 6MWT of Eteplirsen (N = 12) vs External Controls Amenable to Any Exon Skipping (N = 50)

A secondary external control group included a broader DMD population as it included patients amenable to any type of exon skipping therapy, including 8 patients amenable to exon 44

skipping, a milder form of DMD. An analysis between eteplirsen (N = 12) and this larger secondary control group (N=50) amenable to any exon skipping was conducted through Year 3, as data was available through Year 3 only. Notwithstanding comparison to a larger group including milder patients, eteplirsen-treated boys continued to demonstrate a substantive advantage of 79 meters on the 6MWT at Year 3 (p=0.062). As shown in Figure 20, the two patient groups walked comparable mean distances at Baseline and demonstrated similar disease progression trajectories through Year 1. After Year 1, however, they began to diverge, with the eteplirsen-treated patients showing a less severe disease progression, resulting in a clinically relevant difference between the 2 groups by Year 3.

Figure 20: Mean 6MWT Over Time in Eteplirsen-Treated Patients (N=12) vs. Secondary External Controls (N=50, Any Exon Skipping)



† Difference in mean change from baseline at 3 years
 Patients who lost ambulation contributed a score of 0 to the mean

Table 14: Mean 6MWT at Baseline Through Year 4

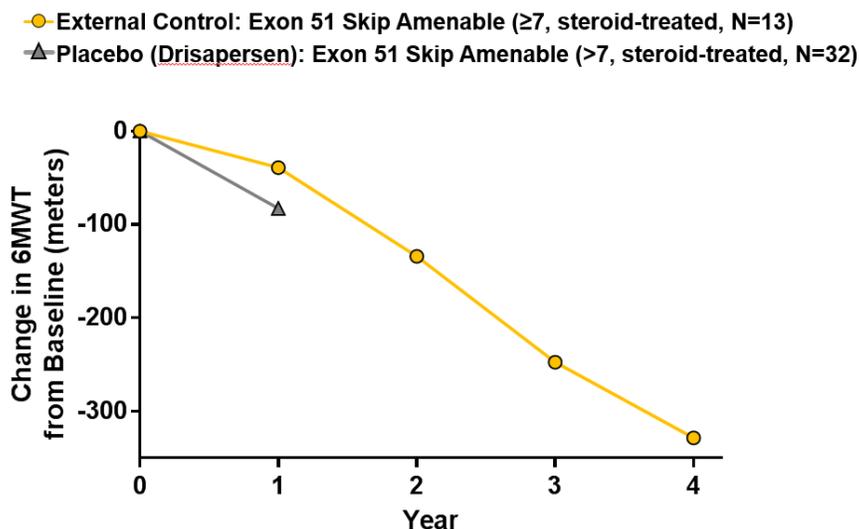
| | Baseline | Year 1 | Year 2 | Year 3 |
|----------------------|---------------|----------------|----------------|----------------|
| Eteplirsen, n | 12 | 12 | 12 | 12 |
| Mean (SD) | 363.2 (42.19) | 305.8 (155.32) | 295.9 (148.98) | 263.1 (151.74) |
| Controls, n | 50 | 50 | 49 | 48 |
| Mean (SD) | 355.7 (87.28) | 313.8 (120.02) | 246.3 (158.19) | 177.1 (163.55) |

6.6.1.4. Decline of 6MWT for External Control (N = 13) Compared to Published Literature

To evaluate the possibility that the external control group had a worse outcome than would have been expected in a cohort of patients from a randomized clinical trial, comparison of the 6MWT for the external control group to published data from a drisapersen trial was conducted (placebo group N = 32). As shown in [Figure 21](#), the external control group (exon 51 skipping N = 13) declined at a slower rate than the drisapersen placebo cohort over the course of one year (specific data for only placebo patients >7 years of age were unavailable past one year). Both groups included boys >7, who were steroid treated and amenable to exon 51 skipping.

This supports the conclusion that the 6MWT 162 meter difference observed for eteplirsen patients (N = 12) vs the untreated external cohort (N = 13) at Year 4 is attributable to eteplirsen treatment, rather than the chance occurrence of an atypically rapid decline of the external control group.

Figure 21: Comparison of 6MWT Change from Baseline in External Controls (N=13) vs Placebo Arm of Randomized Trial (Drisapersen)



Drisapersen values are LS means from available published data
 External control values are unadjusted means

Source for Drisapersen Placebo: Goemans, et al. Drisapersen Efficacy and Safety in Duchenne Muscular Dystrophy: Results of a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial (Study DMD114044). Late Breaking Oral Presentation, WMS 2013, Asilomar, CA.

6.6.2. Loss of Ambulation (LOA)

Ambulatory compromise and loss of ambulation are hallmarks of the progressive muscle degeneration characteristic of DMD (Bushby 2010a; Ciafaloni 2009; van Ruiten 2014). LOA is a reliable overall indicator of the severity of disease progression and strongly correlates with functional measures such as the 6MWT; it is also less influenced by motivational factors. Furthermore, LOA predicts other major disease milestones such as the need for ventilatory support and survival (Bello 2016). Once confined to a wheelchair, other symptoms tend to follow in rapid succession including loss of upper limb function, such that self-care, unsupported sitting, and eating become impaired, severely affecting patient quality of life, as well as that of caregiver and families (Bendixen 2012; Bendixen 2014; Magliano 2014; Uzark 2012). Moreover loss of ambulation is associated with an earlier need for ventilation and premature death (Bushby 2010a; Humbertclaude 2012; Kinali 2007; Van Essen 2004).

In comparison of eteplirsen to the primary external control (N=13) over 4 years, only 2 out of 12 eteplirsen-treated boys lost ambulation compared to 10 of the 13 untreated external control boys amenable to exon 51 skipping therapy. There were two patients missing data at Year 4 but subsequently lost ambulation at ~4.5 years (Patients ECM2 and ECG3). Patient ECM8 who was ambulatory at Year 4 became non-ambulant at Year 4.8.

In comparison of eteplirsen to the secondary external control (N=50), 18 of the 50 untreated external controls amenable to any exon skipping therapy (N=50) lost ambulation; Year 4 data was not available for the larger external control group (Table 15).

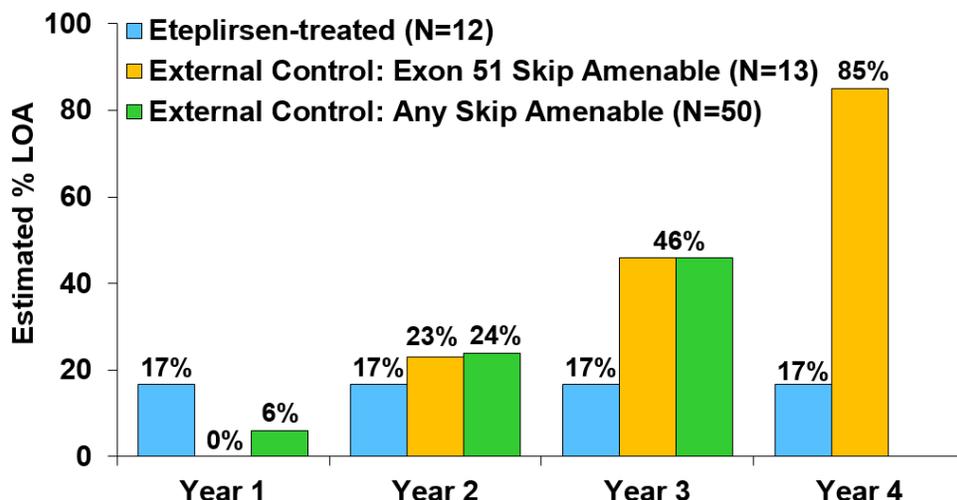
Table 15: Cumulative Loss of Ambulation

| | Year 1 | Year 2 | Year 3 | Year 4 |
|-----------------------------------|--------|--------|--------|--------|
| Eteplirsen (N=12) | 2/12 | 2/12 | 2/12 | 2/12 |
| Primary External Control (N=13) | 0/13 | 3/13 | 6/13 | 10/13 |
| Secondary External Control (N=50) | 3/50 | 12/50 | 18/50 | N/A |

6.6.2.1. Kaplan-Meier Analysis of Loss of Ambulation

A Kaplan-Meier analysis of loss of ambulation (Figure 22), accounting for missing data, estimates that the rate of loss of ambulation over 4 years for the eteplirsen treated boys was approximately 17% compared to 85% (p=0.011) for the primary external control group (N=13). In the more conservative comparison to the external control group amenable to any exon skipping (N=50), the analysis estimated a 3-year loss of ambulation rate of 46% for this secondary external control group.

Figure 22: Kaplan-Meier Estimates of Loss of Ambulation Over 4 Years in Eteplirsen-Treated Patients vs. Primary External Control (N=13) and Over 3 Years vs. Secondary External Control (N=50)



6.6.2.2. Loss of Ambulation of External Control Group Compared to Published Literature

Loss of ambulation observed in the external control group amenable to exon 51 skipping (N=13) is consistent with published literature. In review of 4 recent international publications regarding DMD with any type of mutation, the median age for loss of ambulation ranged from approximately 11 to 13 years of age (Ricotti 2015; Bello 2015, Goemans 2013, Takeuchi 2013). In a recent CINRG publication, a sub-group of glucocorticoid treated patients with DMD amenable to exon 51 skipping (N=32) had a median age at loss of ambulation of 13 years (Bello 2016). These literature sources characterizing the median age at loss of ambulation in DMD are consistent with the observed median age at loss of ambulation observed for the external control group (N = 13) which was 12.9 years. The median age at loss of ambulation for the eteplirsen group is unknown as it has not been reached at Year 4.

Further, two literature sources describe projections for loss of ambulation across age groups, including older boys with genetically confirmed DMD. In a cohort of 242 boys on prednisolone, the median age at LOA was determined to be 11 years (Takeuchi 2013). In another glucocorticoid-treated population (N=65), 90% of which were treated with daily deflazacort, boys experienced a precipitous decline from 12.5 years onwards. For subjects 13.5 years and older, only 13.8% of patients were able to walk with no ambulatory boys by age 15.5 years (Goemans 2013).

For context, the eteplirsen-treated boys (N=12) at Year 4 had a median age of 13.1 with a median age of 13.0 for the 10 ambulatory boys. It is noted that at Year 4, 10 of 12 eteplirsen-treated boys remain ambulant, including 4 over the age of 14.

6.6.3. North Star Ambulatory Assessment (NSAA)

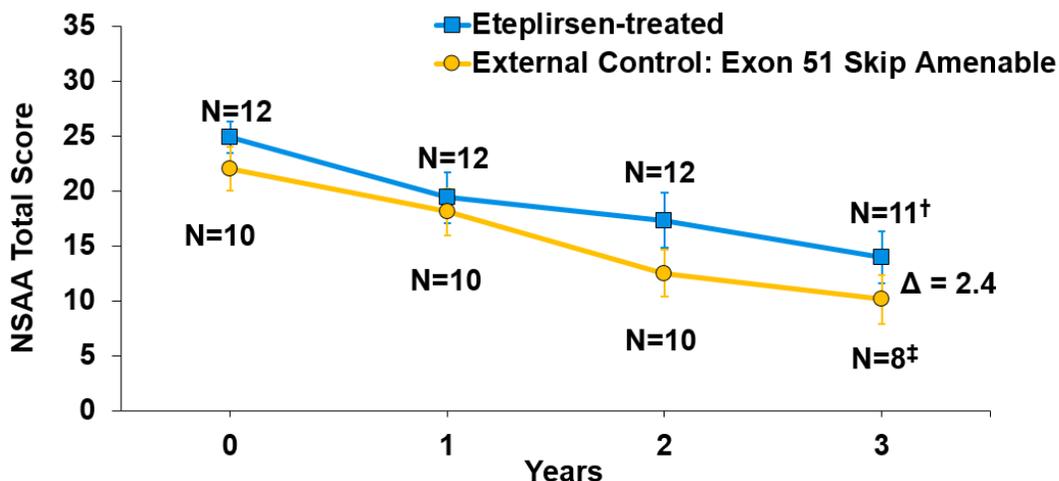
The NSAA is a clinician-reported outcome instrument specifically designed to measure ambulatory function in patients with DMD (Scott 2012). In contrast to the 6MWT, which is a continuous measure, the NSAA is a multiple-item rating scale (17 items) that includes 3 ordered response categories (2, 1, or 0). Items are scored either 2 ('normal' with no obvious modification of activity), 1 (modified method but achieves goal), or 0 (unable to achieve independently). A total 'ambulatory function' composite score is generated by summing items. The 17 items assessed include a 10-meter walk/run, rising from a sit to stand, standing on 1 leg, climbing and descending a step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. The NSAA has undergone detailed psychometric evaluations based on traditional (reliability and validity) and modern (Rasch) methods, and has been included in international DMD clinical trials and natural history studies (Mazzone 2009; Mazzone 2010; Scott 2012; Mayhew 2011). A listing of the 17 items in the NSAA is provided in Appendix 9.

NSAA data (total scores) from eteplirsen-treated patients in Studies 201/202 were compared with longitudinal data from an external cohort. In both the eteplirsen-treated and external control patients, the NSAA was performed according to published methods (Mazzone 2009).

The NSAA results are supportive and directionally consistent with the 6MWT results. NSAA data from eteplirsen-treated patients in Studies 201/202 were compared with 3 year data from the Italian Telethon registry patients amenable to exon 51 skipping (N = 10). As shown in Figure 23, eteplirsen-treated patients had a total score of 24.9 at baseline compared to a score of 22.0 for the external control group, representing a difference of 2.9 at baseline. Over the first year, both the eteplirsen treated boys and the external group declined in function. However, as with the 6MWT, following Year 1, the decline in function for the eteplirsen group became slower. At the end of Year 3, there was a total mean score of 14.0 for the eteplirsen boys representing a mean change of 11.3. For the external control boys the mean score of 10.1 at Year 3 represented a mean decrease of 13.6 from baseline. Overall the untreated external control experienced a greater decrease in change from baseline of 2.4 points relative to eteplirsen treated boys. This is of relevance given that a 2-point decrease in NSAA total score may represent a loss of an activity of daily living.

The NSAA scores for eteplirsen-treated patients vs external control boys at baseline through Year 3 are presented in Figure 23 and Table 16. Appendix 6 provides individual total NSAA scores.

Figure 23: Mean Change in NSAA from Baseline at 3 Years Eteplirsen-Treated (N=12) vs Italian Telethon (N=10)



† 1 eteplirsen patient did not contribute data due to right knee pain

‡ 2 Italian Telethon patients had missing data and were noted to have LOA at this time

Table 16: Mean NSAA Total Scores at Baseline Through Year 3

| | Baseline | Year 1 | Year 2 | Year 3 |
|----------------------|-------------|-------------|-------------|-------------|
| Eteplirsen, n | 12 | 12 | 12 | 11 |
| Mean (SD) | 24.9 (4.93) | 19.4 (7.99) | 17.3 (8.55) | 14.0 (7.80) |
| Controls, n | 10 | 10 | 10 | 8 |
| Mean (SD) | 22.0 (6.27) | 18.1 (6.74) | 12.5 (6.69) | 10.1 (6.17) |

6.6.3.1. Eteplirsen Patients with NSAA Scores ≤ 9 by Year 3, Ambulant at Year 4

The literature suggest that NSAA scores of 9 or below have been associated with a high risk of loss of ambulation within 1 year (Ricotti 2015). As can be seen in Table 17, 4 eteplirsen treated patients had a Year 3 NSAA score of 9 or below. Two of these patients experienced rapid ambulatory decline prior to dystrophin production at week 24 (patients 009, 010). Of the two remaining ambulant boys, despite NSAA score of 9 or below by Year 3, both remain ambulant at Year 4.

Table 17: Eteplirsen-Treated Patients: Year 3 NSAA Score vs. Year 4 6MWT Distance

| Patient ID | Year 3 NSAA Score | Year 4 6MWT Distance (m) |
|------------|-------------------|--------------------------|
| 009 | N/A | 0 |
| 010 | 1 | 0 |
| 003 | 7 | 192 |
| 005 | 8 | 143 |
| 012 | 11 | 237 |
| 007 | 13 | 197 |
| 008 | 13 | 55 |
| 006 | 13 | 332 |
| 013 | 14 | 230 |
| 004 | 24 | 221 |
| 015 | 25 | 400 |
| 002 | 25 | 349 |

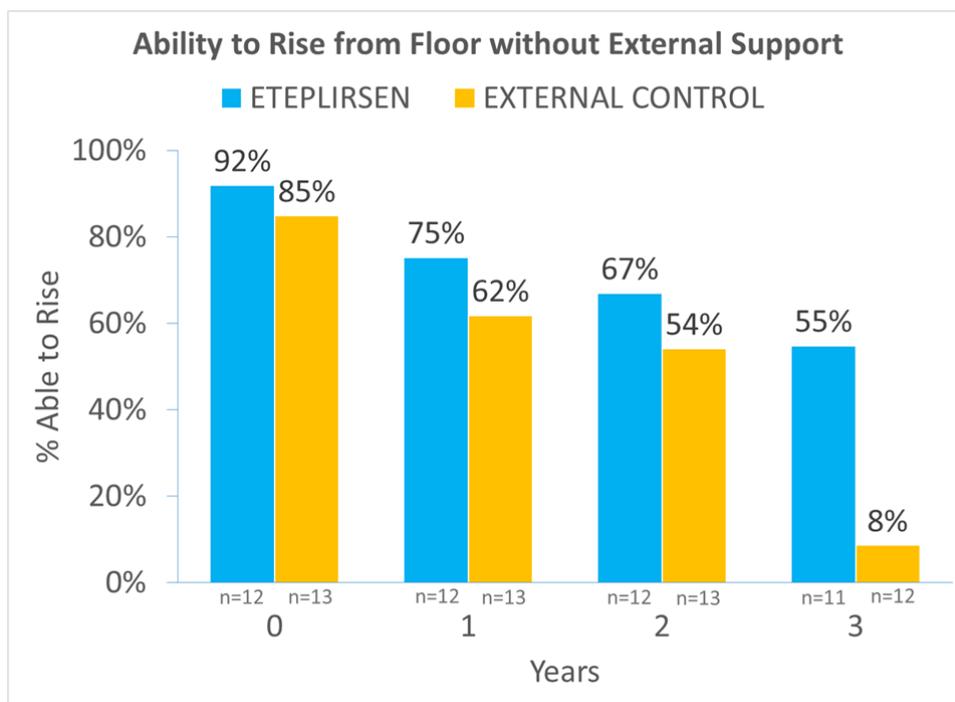
6.6.4. Ability to Rise

The ability to rise from supine is a critical activity for DMD patients and one of the early abilities to be lost in DMD. Loss of ability to rise has been considered to be predictive of subsequent loss of ambulation.

The proportion of eteplirsen (N = 12) vs external control patients (N = 13) who were able to rise at baseline (Year 0) and Year 1, 2 and 3 was calculated. At baseline, 92% of eteplirsen treated patients vs 85% of the external control patients had the ability to rise independently. However by the end of Year 3, 55% of eteplirsen treated boys had maintained the ability to rise, compared to only 8% of the external control patients as illustrated in [Figure 24](#).

The analysis of ability to rise is directionally consistent with 6MWT and LOA data and further supports Eteplirsen’s impact on delaying disease progression.

Figure 24: Eteplirsen Treated Patients (N = 12) vs. External Control Amenable to Exon 51 Skipping (N = 13) Ability to Rise without External Support



6.6.4.1. Eteplirsen Patients Unable to Rise Independently by Year 3, Ambulant at Year 4

Loss of ability to rise independently may be associated with subsequent loss of ambulation within the following 1 to 2 years¹. As can be seen in Table 18, 6 eteplirsen treated patients lost the ability to rise without external support by Year 3. Two of these patients experienced rapid ambulatory decline prior to dystrophin production at week 24 (009, 010). Of the four remaining ambulant boys, despite the eventual loss of ability to rise from supine all remain ambulant at Year 4. Of note, two of these patients (005 and 012) remained ambulant 2 and 3 years respectively after loss of ability to rise. Although limited, these data suggest eteplirsen treated boys are not necessarily losing ambulation in the 1 to 2 year time-frame following the loss of ability to rise independently.

¹ FDA Briefing Document, Peripheral and Central Nervous System Drugs Advisory Committee Meeting, January 22, 2016, NDA 206488 Eteplirsen

Table 18: Eteplirsen Ability to Rise by Year 3 vs. Year 4 6MWT Distance

| Patient ID | Rise w/o External Support (Date if Lost) | Year 3 Rise Time (s) w/o External Support | Year 4 6MWT Distance (m) |
|------------|---|---|-----------------------------|
| 009 | No (Wk 12) | N/A | 0 |
| 010 | No (Wk 4) | N/A | 0 |
| 012 | No (Yr 1) | N/A | 237 |
| 005 | No (Yr 2) | N/A | 143 |
| 003 | No (Yr 3) | N/A | 192 |
| 007 | No (Yr 3) | N/A | 197 |
| 013 | Yes | 24.1 | 230 |
| 006* | Yes | 17.9 | 332 |
| 004 | Yes | 13.1 | 221 |
| 008 | Yes | 8.9 | 55+ |
| 015 | Yes | 8.2 | 400 |
| 002 | Yes | 6.2 | 349 |

*Patient 006 unable to rise w/o external support at BL but subsequently had ability

†Patient 008 had a tibia fibula fracture at week 84

6.6.5. Pulmonary Function Tests

Respiratory function in DMD is progressively impaired over time as the dystrophic process affects respiratory muscles, including the diaphragm, and leads to significant morbidity and mortality. Respiratory function is measured by pulmonary function testing (PFTs), which includes measurement of lung volume (forced vital capacity, FVC) and the ability to generate pressure during inspiration (maximum inspiratory pressure, MIP) and expiration (maximum expiratory pressure, MEP).

FVC measures integrity of both inspiratory and expiratory muscles, is an excellent measure of respiratory function reserve, and is widely used in DMD to assess respiratory muscle function. Most studies that define the natural history of PFTs in patients with DMD include measurement of FVC, and therefore FVC provides the best available comparator for patients treated with eteplirsen (Mayer 2015; Buyse 2015; Khirani 2014; Henricson 2013; Hahn 1997; McDonald 1995; Miller 2005). MEP and MIP are also used as measures of expiratory and inspiratory muscle function, respectively, in neuromuscular diseases including DMD (Khirani 2014; Henricson 2013; Hahn 1997). MEP and MIP are indicators of decreased respiratory muscle strength, but are subject to variability given that patients with muscle weakness and especially very young patients may have a reduced ability to perform the tests correctly.

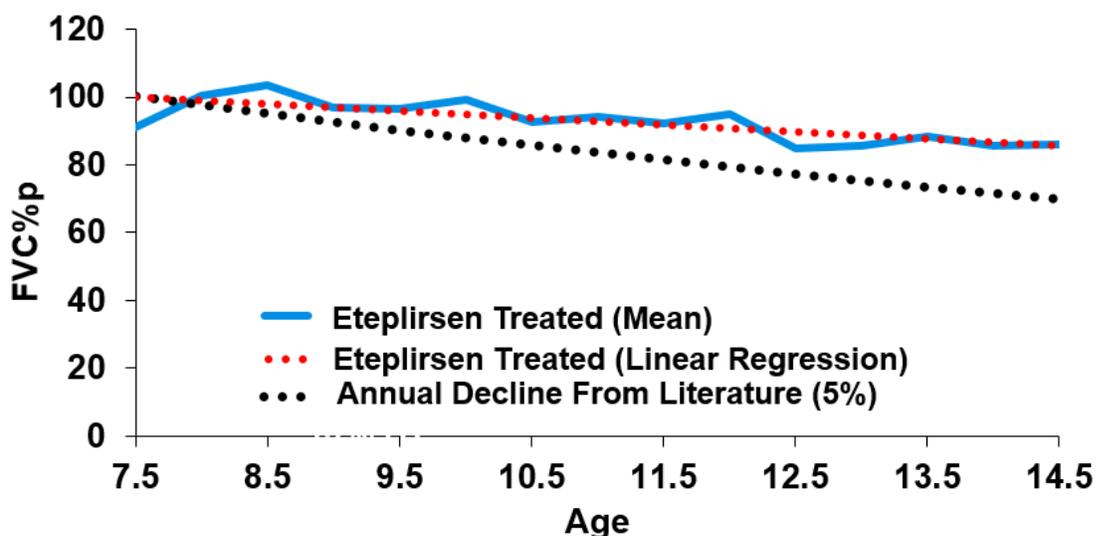
Measurements of PFTs such as volume (FVC) or pressure (MEP and MIP) are converted to values relative to normal (% predicted). PFT values in adults decline with age. In children, in contrast, there is a dramatic increase in PFT parameters over time, which parallels increases in height and age. Hence, a correction factor accounting for growth/age needs to be incorporated for calculation of predicted values in the pediatric population. The methodology for calculation of

predicted FVC values was described by Polgar (Polgar 1971) and corrects based on height. The most widely used correction for predicting MEP and MIP, which adjusts by age (MEP) or weight (MIP), was established by Wilson (Wilson 1984).

The majority of contemporary published data evaluating FVC% predicted, suggest a linear decline of at least 5% annually (Mayer 2015; Buyse 2015; Khirani 2014; Henricson 2013). Mayer et al have postulated that neither corticosteroid treatment nor ambulatory status affect the annual decline rate of 5% in FVC% predicted (Mayer 2015).

In eteplirsen treated patients, mean FVC% predicted decreased from 97.7% to 89.4% over 168 weeks, i.e. a decrease of 2.4% per year. In an analysis of FVC % predicted by age rather than time on study, a 2.5% decrease per year was demonstrated. This decrease of approximately 2.5% per year compares favorably with the expected $\geq 5\%$ decrease in FVC% predicted that has been observed in natural history studies of DMD (Figure 25).

Figure 25: FVC % Predicted (FVC%p) in Eteplirsen-Treated Patients vs. Age



Measurement of MIP and MEP has been done in patients with DMD, albeit to a lesser extent than FVC, and only 3 relevant scientific publications have been identified (Khirani 2014; Hahn 1997; Henricson 2013). Based on these data, an annual decline of MIP% predicted and MEP% predicted of approximately 3-4% would be expected in patients with DMD during their second decade. The change from baseline over 3 years with eteplirsen treatment is -3.6% for MIP% predicted and -8.4% for MEP% predicted, which translates into a decrease of 1% and 2.4%, per year, respectively). Interpretation of MIP and MEP data is limited by the small number of scientific publications describing these specific assessments in DMD and the increased effort dependency compared to FVC for assessment of MIP and MEP, leading to higher variability especially in a pediatric population.

In summary, pulmonary function data from DMD patients who received eteplirsen over 168 weeks were compared to data from the scientific literature. The deterioration of respiratory muscle function as measured by FVC% predicted appears to be slower than expected with eteplirsen treatment. Additionally, MEP% predicted and MIP% predicted were evaluated, and while natural history data are limited, these data appear supportive of the FVC% predicted results.

7. PHARMACODYNAMIC RESULTS

7.1. Methods for Assessing Pharmacodynamic Endpoints

Several complementary methods were used to provide a detailed assessment of eteplirsen's effects on exon skipping and dystrophin protein expression, as no single measurement of dystrophin production can provide a complete evaluation of eteplirsen's pharmacodynamic and biological effects. In the eteplirsen clinical program, the evaluation of exon skipping was accomplished by RT-PCR and sequencing of the PCR product. Dystrophin protein production was evaluated by assessment of the percent dystrophin positive fibers and dystrophin intensity in histological specimens, and by Western blot.

Overall, in the 4 studies evaluating pharmacodynamics endpoints, there was a high ascertainment rate with all muscle biopsies resulting in evaluable samples. In Studies 201/202, analysis of muscle tissue 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. This original analysis was performed at Nationwide Children's Hospital in Columbus, OH. In response to FDA concerns regarding analysis at a single site, an independent re-analysis of percent dystrophin positive fibers, was performed at a second site by three independent pathologists. Biopsy processing and analysis of samples for Studies 28 and 33 were performed at a separate laboratory. A high-level summary of the methods used to evaluate exon skipping and dystrophin production as well as study specific biopsy schedules are summarized in [Table 19](#).

Table 19: Methods for Evaluation of Pharmacodynamic/Biologic Endpoints by Studies

| | Study 33 | Study 28 | Study 201/202 |
|--|--|--|--|
| Anatomic Location of Muscle Biopsy | Extensor digitorum brevis muscle of treated and opposite placebo foot at baseline and Day 14-28 | Biceps brachii Biopsy samples at baseline and Week 14 | Biceps brachii (Baseline and Week 24) and deltoid biopsy samples (Week 48 and Week 180) |
| <i>Mechanism of Action Confirmation</i> | | | |
| Detection of internally deleted dystrophin mRNA | RT-PCR assessment of mRNA exon 51 skipping | RT-PCR assessment of mRNA exon 51 skipping | RT-PCR assessment of mRNA exon 51 skipping |
| Sequencing of mRNA to confirm correct exon skipping | Direct sequencing of RT-PCR product | Direct sequencing of RT-PCR product | Direct sequencing of the RT-PCR product (Week 180 only) |
| <i>Dystrophin Production and Localization</i> | | | |
| Dystrophin protein levels | Western Blot assessment of Dystrophin protein levels with NCL-DYS1 ^a | Western Blot assessment of Dystrophin protein levels with NCL-DYS1 ^a | Western Blot assessment of Dystrophin protein levels with MANDYS106 ^a , NCL-DYS2 ^a and NCL-DYS1 ^a (Week 180 only) |
| Percent dystrophin positive muscle fibers | Scoring of digital images for presence of dystrophin-positive muscle fibers following indirect immunofluorescence staining with MANDYS106 ^a | Scoring of digital images for presence of dystrophin positive muscle fibers following indirect immunofluorescence staining with MANDYS106 ^a | Scoring of digital images for presence of dystrophin positive muscle fibers following indirect immunofluorescence staining with MANDYS106 ^a , NCL-DYS2 ^a , NCL-DYS3 ^a |
| Dystrophin Intensity | Assessment of fluorescence signal intensity following indirect immunofluorescence staining with MANDYS106 ^a antibody against dystrophin | Assessment of fluorescence signal intensity following indirect immunofluorescence staining with MANDYS106 ^a antibody against dystrophin | Assessment of fluorescence signal intensity following indirect immunofluorescence staining with MANDYS106 ^a , NCL-DYS2 ^a antibody against dystrophin |

^a Dys1: NCL-DYS 1 Clone Dy4/6D3 (Leica); Dys2: NCL-DYS 2 Clone DY8/6C5; MANDYS106: [Nguyen 1992](#).

7.2. Pharmacodynamic/Biological Endpoints

7.2.1. RT-PCR Demonstrates Exon 51 Skipping in Studies 201/202, 28 and 33

All studies used qualitative nested end-point RT-PCR to detect the presence or absence of internally shortened dystrophin mRNA to confirm exon 51 skipping. PCR primers were specific for each patient's known dystrophin mutation, and RT-PCR products were visualized on agarose gels. In addition, the accurate skipping of exon 51 was confirmed by sequencing of the skipped RT-PCR product in Studies 28 and 33, and for the Week 180 biopsy in Studies 201/202. Exon 51

skipping was demonstrated using RT-PCR in all eteplirsen-treated patients evaluated to date (N = 36).

- **Proof of Concept Study 33:** (N = 7) patients were given a single dose of eteplirsen IM 0.9 (N = 5) or 0.09 mg (N = 2) directly into the EDB muscle and a single dose of placebo in the contralateral foot. RT-PCR demonstrated exon 51 skipping in the eteplirsen-treated foot of all patients, although only low-level exon skipping was observed in the 2 patients receiving the low dose of 0.09 mg.
- **Dose-Ranging Study 28:** (N = 17) patients were given 12 weekly IV doses of eteplirsen (0.5-20 mg/kg/week) with muscle biopsies at baseline and post-treatment Week 14. In this study, exon skipping in post-treatment biopsies was most easily and reliably detected in those patients within the 2 highest dose groups (10 and 20 mg/kg) suggesting a dose-dependent effect of eteplirsen on exon skipping.
- **Pivotal Study 201/202:** (N = 12) tested higher doses of 30 or 50 mg/kg/week with muscle biopsies taken at baseline and on-treatment Week 12, 24, 48 and 180. Exon skipping was observed for all 12 patients.

Skipping of exon 51 was confirmed with Sanger sequencing ([Sanger 1975](#)). Accurate sequences of the flanking DNA at the new exon junction formed by skipping exon 51 were confirmed in all assessed patients from Study 33 (N = 7), Study 28 (N = 17) and Studies 201/202 (Week 180 biopsies only, N = 11). Observed sequences were consistent with those found in BMD patients with the corresponding in-frame mutation, supporting the hypothesis that eteplirsen results in the production of functional dystrophin protein capable of attenuating the DMD phenotype.

7.2.2. Dystrophin Protein Expression – Percent Dystrophin Positive Fibers

Across studies, the production of dystrophin protein pre- and post-treatment was evaluated using immunohistochemical (IHC) methods. The percent dystrophin-positive fibers (PDPF) was determined by pathologist evaluation counting both the number of dystrophin positive muscle fibers and the total number of muscle fibers to allow the calculation of a percent dystrophin positive muscle fibers. In pivotal studies 201/202, treatment with eteplirsen produced reliable increases in the percent dystrophin positive fibers.

7.2.2.1. Study 201/202

The primary endpoint in the 24-week placebo-controlled portion of Study 201 was change from baseline in percent dystrophin positive fibers. At Week 25, the placebo patients were rolled over onto open-label treatment and all patients continue to receive treatment in the on-going extension study today.

A key question that Study 201/202 sought to address, was whether dose or duration was more important in the induction of novel dystrophin protein. Accordingly, while all patients had muscle biopsies at baseline, Week 48 and Week 180, in order to minimize the number of required biopsies, the study design varied the biopsy schedule at Week 12 (only 50 mg/kg and 2 placebo patients) and Week 24 (only 30 mg/kg and 2 placebo patients). [Figure 26](#) displays the biopsy schedule by treatment group in Studies 201/202.

Figure 26: Biopsy Schedule in Studies 201/202

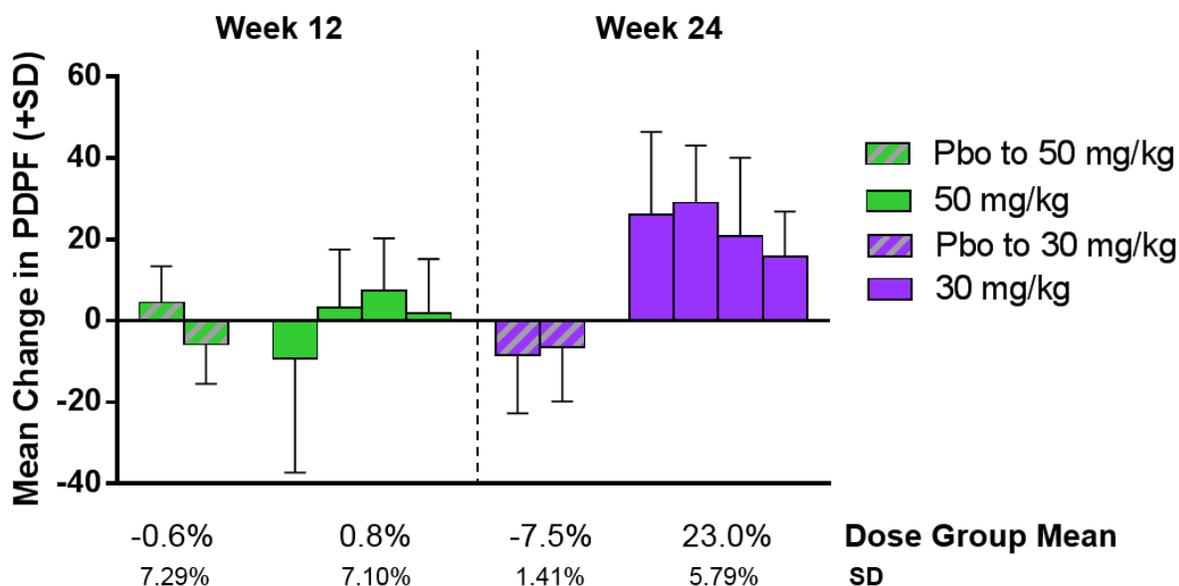
| Treatment Group | Baseline | Week 12 | Week 24 | Week 25 | Week 48 | Week 180 |
|-----------------|----------|---------|---------|--|---------|----------|
| 30 mg/kg | √ | | √ | Placebo patients rolled onto treatment | √ | √ |
| Placebo | √ | | √ | | | |
| 50 mg/kg | √ | √ | | | √ | √* |
| Placebo | √ | √ | | | | |

*1 patient declined the optional Wk 180 biopsy

Treatment with 50 mg/kg did not demonstrate a significant increase in the amount of mean percent dystrophin positive fibers at Week 12. However, treatment with 30 mg/kg eteplirsen (N = 4) for 24 weeks significantly increased the mean percent dystrophin positive fibers from a baseline of 18.19% to 41.14% resulting in an absolute increase of 22.95% baseline $p \leq 0.004$). This change was also statistically significantly different than the change from baseline observed in the placebo-treated patients ($p \leq 0.002$). Mean change from baseline in PDPF for each individual patient is shown in [Figure 27](#).

These results indicate that 12-weeks is an insufficient treatment duration to observe significant dystrophin production, whereas an increase in dystrophin was shown by Week 24.

Figure 27: Individual Patient Data: Mean Change from Baseline in Percent Dystrophin Positive Fibers (MANDYS106) in Patients Treated with 50 or 30 mg/kg Eteplirsen vs. Placebo at Week 12 and 24, respectively (Study 201)

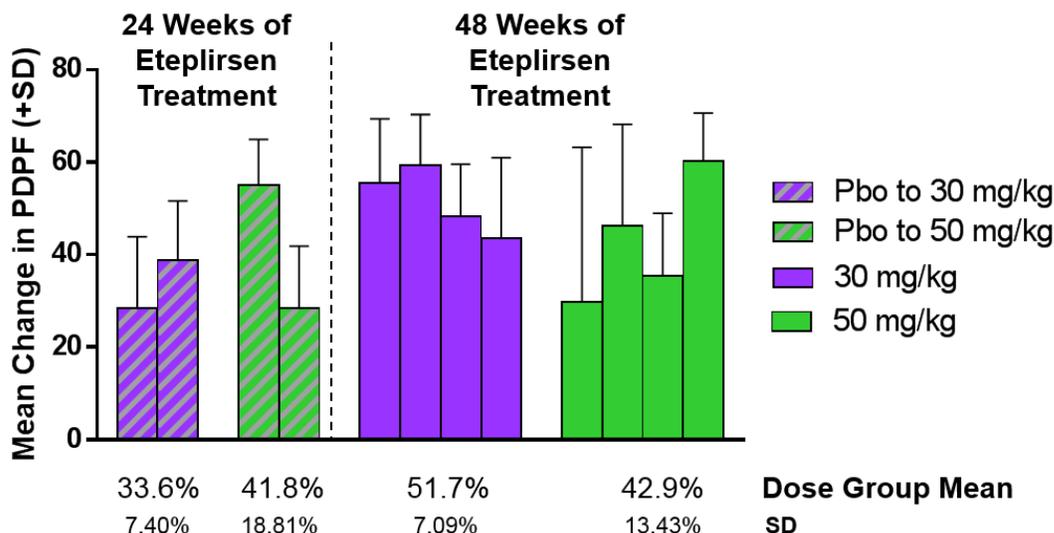


7.2.2.2. Dose selection of 30 mg/kg based on Week 48 analysis of Studies 201/202

Analysis of mean change in percent dystrophin positive fibers at Week 48 showed that both 30 and 50 mg/kg weekly doses significantly increased the mean percent dystrophin positive fibers compared to baseline ($p \leq 0.001$, $p \leq 0.008$, respectively), with no significant difference in the magnitude of this change between the 2 dose groups. Statistically significant changes from baseline were also observed when the dystrophin results at Week 48 were combined for the 4 patients who received placebo for the first 24 weeks ($p \leq 0.009$) and for the 8 patients who received eteplirsen continuously ($p \leq 0.001$). Mean change from baseline in PDPF for each individual patient is shown in [Figure 28](#).

Given the equivalency of Week 48 mean change in PDPF between 30 or 50 mg/kg, and the need for chronic lifelong administration in a pediatric population, the lower dose of 30 mg/kg dose was selected.

Figure 28: Mean Change from Baseline in Percent Dystrophin Positive Fibers in Patients Treated with 30 vs 50 mg/kg/week Eteplirsen for Week 24 or 48 (Studies 201/202)



7.2.2.3. Independent Verification of Percent Dystrophin Positive Fibers

The original analysis of PDPF was performed at Nationwide Children’s Hospital in Columbus, OH by a single pathologist. The FDA expressed concerns regarding analysis from a single site and pathologist. In response to this request by the Agency, the original images used in scoring the percent dystrophin positive fibers in biopsy samples from patients in Studies 201/202 and Study 28 were re-assessed by 3 independent and blinded raters. Per the Agency’s request, the primary endpoint for the image reassessment was the percent dystrophin positive fibers at Week 24 and changes from baseline. Sarepta engaged 3 trained pathologists (through Flagship Biosciences) to independently identify dystrophin positive fibers utilizing the same archived digital images obtained from Study 201 and Study 28 used for the original study assessments.

7.2.2.4. Independent Verification of Study 201/202 Percent Positive Dystrophin Fibers

The mean ratings from the independent pathologists showed the mean percent dystrophin positive fibers for the 4 patients in the 30 mg/kg eteplirsen group increased from 13.63 at baseline to 27.33 at Week 24, representing a 1.37-fold, statistically significant ($p=0.007$) increase, consistent with the results of the original analysis performed at Nationwide Children’s Hospital in Columbus, OH. Evaluation of inter-rater and intra-rater reliability confirmed that consistency was achieved through training of the independent raters. The inter-rater reliability for the 3 blinded pathologists performing the reassessment was high (interclass correlation coefficient [ICC] = 0.793), as was the intra-rater reliability, with ICCs for each rater ranging from 0.932 to 0.955.

7.2.2.5. Study 28 Percent Positive Dystrophin Fibers

Once weekly IV infusions of eteplirsen (0.5 to 20 mg/kg) for 12 weeks in Study 28 resulted in a 3-fold increase in the mean percent dystrophin positive fibers, which increased from a mean of 2.2% at baseline to 6.5% at Week 14 (biopsies were taken 2 weeks after the last dose), with the greatest mean increases observed for highest doses (i.e., 10 or 20 mg/kg), although variation across individual results was noted.

7.2.2.6. Independent Verification of Study 28 Percent Positive Dystrophin Fibers

The original analysis of the percent dystrophin positive fibers, which was performed at the University College London, was also confirmed by a blinded reassessment of the data by 3 independent pathologists, who noted mean increases from 1.83% at baseline to 8.19% at Week 14 for 4 patients who received 10 mg/kg/week and mean increases from 2.87% at baseline to 15.87% at Week 14 for 4 patients who received 20 mg/kg/wk eteplirsen. Although increases in dystrophin were observed as early as 14 weeks in Study 28, this was not consistent across individuals.

7.2.2.7. Study 33 Percent Positive Dystrophin Fibers

Results from Study 33, in which 7 patients received a single IM dose of 0.09 mg (N = 2) or 0.9 mg (N = 5) eteplirsen into the EDB muscle of one foot and a single dose of placebo into the EDB of the opposite foot, further support eteplirsen's ability to induce dystrophin production in patients with DMD. In this study, dystrophin positive fibers were observed in biopsies obtained from the eteplirsen treated feet of the 5 patients who received the higher dose of eteplirsen, 4 of whom were already non-ambulatory at the time of the study. The mean percent dystrophin positive fibers in EDB muscle biopsy specimens from the eteplirsen-treated feet was 59.7% compared with 0% in EDB muscle biopsy specimens from the placebo-treated feet of the same 5 patients. The lower dose of eteplirsen (0.09 mg) did not have a measurable effect on dystrophin production in this study

7.2.3. Dystrophin Protein Expression – Dystrophin Fiber Intensity

Analysis of dystrophin fiber intensity as measured by an automated software system (Bioquant[®] or MetaMorph[®]) was used as a complementary method to verify the *de novo* production of dystrophin. In Studies 201/202, 28 and 33, eteplirsen's effect on dystrophin production was examined by measuring the fluorescence staining intensity of dystrophin following indirect immunostaining with primary anti-dystrophin antibodies. In both studies, the mean changes from baseline in dystrophin fiber intensity were similar in magnitude and direction to the results of the percentage of dystrophin positive fibers analyses, supporting eteplirsen's ability to increase dystrophin levels in patients with DMD.

7.2.3.1. Studies 201/202 Dystrophin Intensity

Once weekly treatment with eteplirsen (30 or 50 mg/kg) significantly increased ($p \leq 0.001$) mean dystrophin fiber intensity from 10.57% of normal at baseline to 25.98% of normal at Week 48 in the 8 patients in Studies 201/202 who received eteplirsen from the start of the study. Eteplirsen also significantly ($p \leq 0.006$) increased mean dystrophin fiber intensity from 8.95% of normal at baseline to 23.43% of normal at Week 48 in the 4 patients in Studies 201/202 who received

placebo from baseline to Week 24 and eteplirsen from Weeks 24 to 48 (and hence had only received eteplirsen for 24 weeks at the time of the Week 48 biopsy).

7.2.3.2. Study 28 Dystrophin Intensity

Similarly, in Study 28, once weekly treatment with eteplirsen increased mean dystrophin fiber intensity in the 17 patients with evaluable data from 7.9% of normal at baseline to 11.5% of normal at Week 14. The results were variable within and across dose groups, but the largest and most consistent increases tended to occur in the 10 and 20 mg/kg/wk eteplirsen groups.

7.2.3.3. Study 33 Dystrophin Intensity

In Study 33, a single IM dose of 0.9 mg eteplirsen increased the mean dystrophin fiber intensity from 9.4 % in the contralateral saline-injected muscle to 26.4% in the eteplirsen-treated muscle. The lower dose of eteplirsen (0.09 mg) did not have a measurable effect on dystrophin production in this study.

7.2.4. Dystrophin Quantity By Western Blot

7.2.4.1. Study 33, 28 Western Blot

Dystrophin expression was also evaluated by Western Blot in Studies 33, 28 and 201/202. In Study 28, the most consistent increase in dystrophin expression from baseline tended to occur in the 10 and 20 mg/kg/wk eteplirsen group. Similarly, the higher dose group in Study 33 showed a more consistent expression above baseline than the lower dose group. Results for Study 201/202 are presented in the Week 180 section below.

7.2.5. Studies 201/202: Week 180 Results For Dystrophin Production

Patients in Studies 201/202 underwent a fourth muscle biopsy after 180 weeks in the study. The primary purpose of this optional biopsy was to evaluate the ability of eteplirsen to sustain dystrophin production during chronic treatment. This biopsy also afforded an opportunity to examine dystrophin production using the optimized method previously described for evaluation of percent dystrophin positive fibers. In addition, new Western blot methodology was developed in alignment with the NIH-FDA Dystrophin Methodology Workshop (March 2015) and in consultation with the FDA.

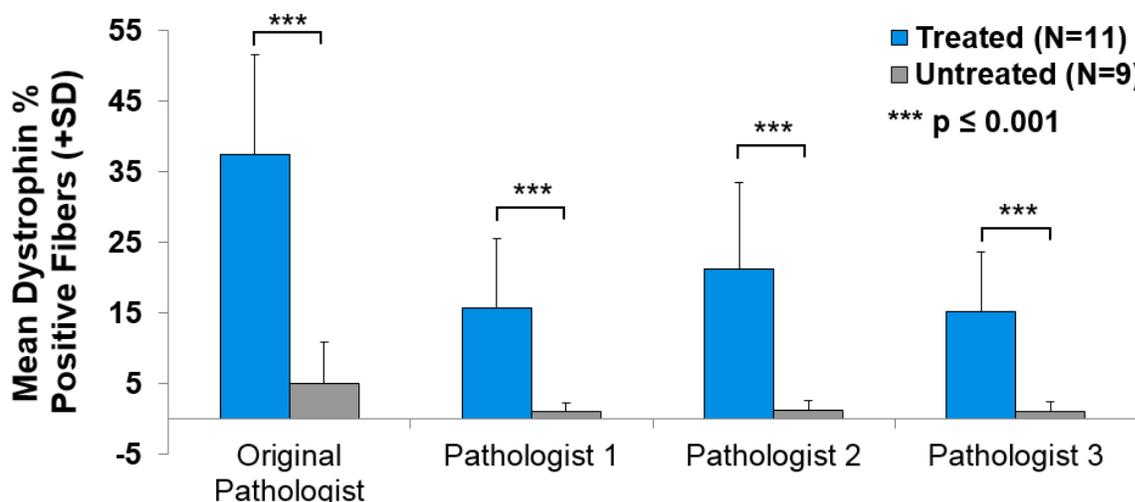
Eleven of the 12 patients provided muscle biopsies at Week 180. As mentioned previously, it is important that biopsy results be compared to pre-treatment or untreated controls in order to evaluate the treatment effect on dystrophin expression. Frozen, archived baseline muscle biopsy tissue from Study 201 was available for re-analyses from only a limited number of patients, resulting in baseline values for only 3 patients for each of the 3 dystrophin parameters. Since baseline tissue was not available for all patients, these samples were supplemented with tissue from untreated control patients amenable to exon 51 skipping in order to provide a total of 9 untreated samples as a comparator group. The additional 6 untreated control samples for each assay were from confirmatory Study 301 (PROMOVI) and were simply the first baseline biopsies collected that had sufficient excess biopsy material available to repurpose for use in the Week 180 analysis. Characteristics for the untreated control patients are summarized in [Appendix 10](#).

Biopsies were evaluated by three complementary methods: scoring of digital images for the percent dystrophin positive fibers following indirect immunofluorescence staining; BIOQUANT[®] assessment of dystrophin fiber intensity following indirect immunofluorescence staining; and Western blot assessment of dystrophin protein levels.

7.2.5.1. Study 201/202 Week 180 Percent Dystrophin-Positive Fibers (PDPF)

As shown in Figure 29, the mean percent dystrophin positive fibers in the eteplirsen-treated patients at Week 180 (37.33%), as determined by a blinded analysis of digital images performed by the expert pathologist at NCH, was 7.4 times greater than that observed in untreated patients (5.04%), a difference that was statistically significant ($p < 0.001$). Confirmation of this finding (treated PDPF > untreated PDPF) was provided by an independent analysis of identical images conducted by 3 blinded independent pathologists, with mean differences between the eteplirsen-treated patients and the untreated controls ranging from 14.15% to 19.99% for the 3 raters (all p -values < 0.001). Refer to Appendix 11 for individual patient PDPF data and Appendix 13 for representative images of dystrophin-positive fibers.

Figure 29: Mean Percent Dystrophin-Positive Fibers in Eteplirsen-Treated Patients (Week 180, Studies 201/202) vs. Untreated DMD Controls



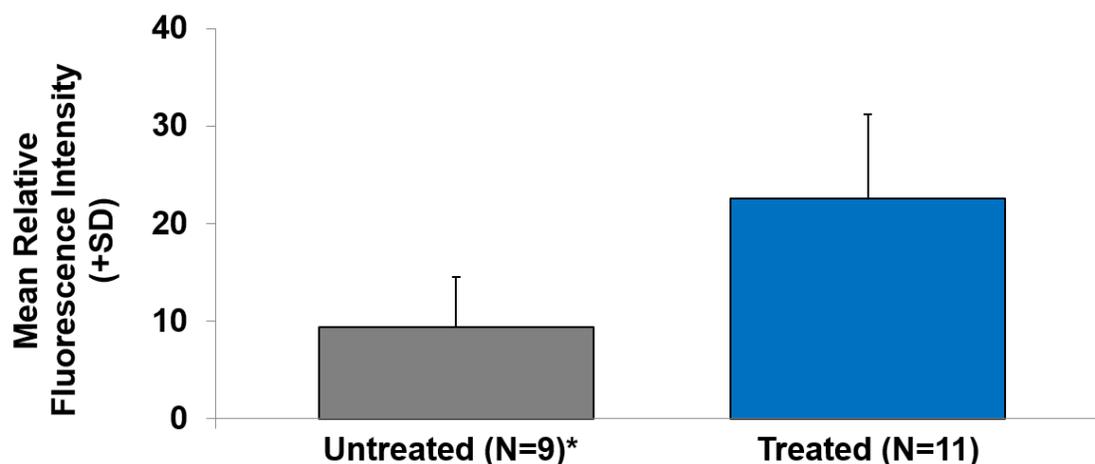
| | Original Assessment | Reassessment | | |
|-----------------------|----------------------|---------------------|----------------------|---------------------|
| | NCH Pathologist | Pathologist 1 | Pathologist 2 | Pathologist 3 |
| Eteplirsen, mean (SD) | 37.33 (14.267) | 15.67 (9.846) | 21.30 (12.219) | 15.20 (8.442) |
| Untreated, mean (SD) | 5.04 (5.85) | 1.02 (1.293) | 1.31 (1.294) | 1.05 (1.371) |
| Mean Diff. (95% CI) | 32.29 (22.15, 42.43) | 14.66 (8.01, 21.30) | 19.99 (11.75, 28.22) | 14.15 (8.44, 19.87) |
| p-value | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ |

| Pathologist(s) | Absolute Difference of Mean PDPF (Treated vs. Untreated) | Fold Increase (Treated vs. Untreated) | p-value |
|-----------------|--|---------------------------------------|-----------|
| Multi-rater (3) | 16.27% | 15.5 | < 0.001 |

7.2.5.2. Study 201/202 Week 180 Dystrophin Intensity

The IHC images were also evaluated by an automated computer algorithm to assess for dystrophin staining intensity. Generally higher dystrophin staining was observed for individual eteplirsen-treated patients in comparison to untreated control patients, with the overall mean dystrophin fiber intensity in eteplirsen-treated patients at Week 180 (22.61) significantly ($p < 0.001$) greater than that observed in untreated controls (9.41) as shown in [Figure 30](#), [Table 20](#). Results for dystrophin fiber intensity from individual patients are provided in [Appendix 12](#).

Figure 30: Mean Dystrophin Intensity in Eteplirsen-Treated Patients (Week 180, Studies 201/202) vs. Untreated DMD Controls



*N = 3 201/202 baseline + N = 6 confirmatory study baseline

Table 20: Absolute and Relative Differences of Mean Dystrophin Intensity (Week 180, Studies 201/202)

| Absolute Difference of Mean Intensity (Treated vs. Untreated) | Fold Increase (Treated vs. Untreated) | p-value |
|---|---------------------------------------|---------|
| 13.2% | 2.4 | <0.001 |

7.2.5.3. Study 201/202 Week 180 Western Blot

Sarepta, in consultation with the FDA and in alignment with the FDA-NIH Dystrophin Methodology Workshop (March 2015), developed a robust Western blot assay for quantification of dystrophin protein in muscle tissue. The validated Western blot assay used for Week 180 analysis included a 5-point standard curve on every gel that was within the dynamic range of the assay, enabling sensitive and accurate quantitation of dystrophin as low as 0.25% of normal. Western Blot method validation and acceptance standards are detailed in [Appendix 15](#) along with representative gel images.

In order to evaluate a treatment effect it is imperative to compare treated patient biopsies to untreated DMD controls. Comparison to literature values is inappropriate because historical Western blot assays in the majority of publications were not performed within a dynamic range, lacked the necessary controls to accurately quantify dystrophin, and at best were qualitative

approximations. In the absence of a valid comparator from the published literature, Week 180 and untreated DMD tissue controls were randomized, blinded and measured relative to a “normal” tissue control.

A universal dystrophin reference standard does not exist. In its absence “normal” muscle biopsy tissues are used, however there can be inherent variation in dystrophin levels between individuals of more than two fold [FDA-NIH Dystrophin Methodology Workshop (March 2015) and eteplirsen NDA 206,488]. Therefore a single “normal” tissue control (non BMD/DMD) was used as a relative reference standard to ensure consistent and accurate quantification of dystrophin in the eteplirsen treated and untreated samples. This “normal” biopsy tissue was used to prepare the 5-point calibration curve that was run on each gel to calculate dystrophin as % of normal.

Baseline/untreated dystrophin levels were assessed using baseline biopsy tissue from 201/202 patients (available for 3 patients) or obtained from patients in the eteplirsen Phase 3 confirmatory study (PROMOVI). The patients in the PROMOVI study are closely matched in their baseline characteristics (exon 51 amenable mutation, age and ambulation) to Study 201/202 patients. These baseline/untreated samples were blinded and randomized with the Week 180 eteplirsen treated samples, thus providing a robust, internal comparator for measurement of the fold increase in novel dystrophin production. Of note, the dystrophin levels observed for all baseline/untreated samples were comparable, whether from 201/202 patients or from PROMOVI baseline patients, demonstrating a well-matched baseline comparator for determining fold increase of dystrophin.

In Western blot analysis, 9 of 11 biopsied eteplirsen-treated patients had an observable dystrophin band. For illustrative purposes, an example of baseline (untreated) and Week 180 (eteplirsen-treated) dystrophin band intensity on Western blot gels is shown below in [Figure 31](#).

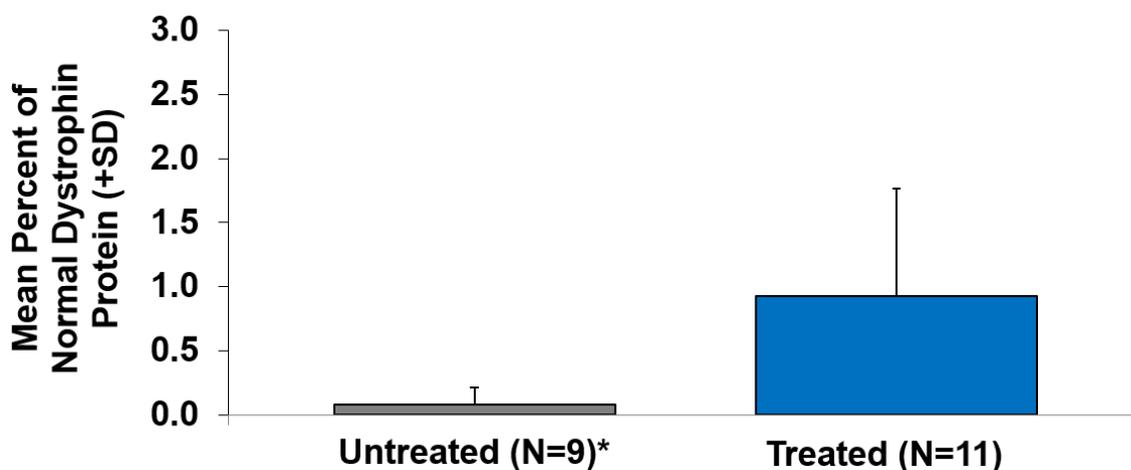
Figure 31: *De Novo* Dystrophin Protein Production after Treatment with Eteplirsen at Week 180

The relevant regions from two Western blot gels illustrates dystrophin absence (BLOQ) in pre-treatment and *de novo* dystrophin production at Week 180 (1.67% of normal) in muscle tissues from the same patient. Unt = DMD untreated control. The 5-point standard curve is 4%-0.25% of normal.

Eteplirsen-treated patients demonstrated a statistically significant ($p=0.007$) higher mean dystrophin expression level compared to untreated controls. The mean dystrophin protein level in eteplirsen-treated patients at Week 180 was 0.93% of normal compared to 0.08% in untreated controls (Figure 32, Table 21), demonstrating an 11.6-fold increase of treated over untreated. Results for Western blot analysis from individual patients are provided in Appendix 14.

While publications citing estimates of dystrophin levels in DMD patients exist, it is critical to note that these cited values are at best approximations and were not measured using assays appropriate for clinical therapeutic assessment. In the absence of a robust measure of the mean dystrophin levels in DMD patients, and given the variability of dystrophin levels associated with genotype, the most robust measure of response to treatment is to compare the internally measured control baseline of 0.08% with the Week 180 treated value of 0.93% of normal, resulting in a 11.6-fold increase from treatment with eteplirsen.

Figure 32: Mean Percent Normal Dystrophin in Eteplirsen-Treated Patients (Week 180, Studies 201/202) vs. Untreated DMD Controls (Western Blot)



*N = 3 201/202 baseline + N = 6 confirmatory study baseline

Table 21: Absolute and Relative Differences of Mean Dystrophin by Western Blot (Week 180, Studies 201/202)

| Absolute Difference of Means (Treated vs. Untreated) | Fold Increase (Treated vs. Untreated) | p-value |
|--|---------------------------------------|---------|
| 0.85% | 11.6 | 0.007 |

7.2.5.4. Summary Week 180 Data

A statistically significant fold increase in dystrophin following treatment was demonstrated by three complementary assays, as highlighted by the Week 180 biopsy results detailed in Table 22. In addition, correct localization at the sarcolemmal membrane was confirmed by immunohistochemistry (percent dystrophin-positive fibers [PDPF]). Consistent with literature reports (Taylor 2012, Anthony 2012a), a strong correlation is seen for dystrophin quantitation by fiber intensity and Western blot (Pearson Correlation Coefficient = 0.709; p -value = 0.015) as

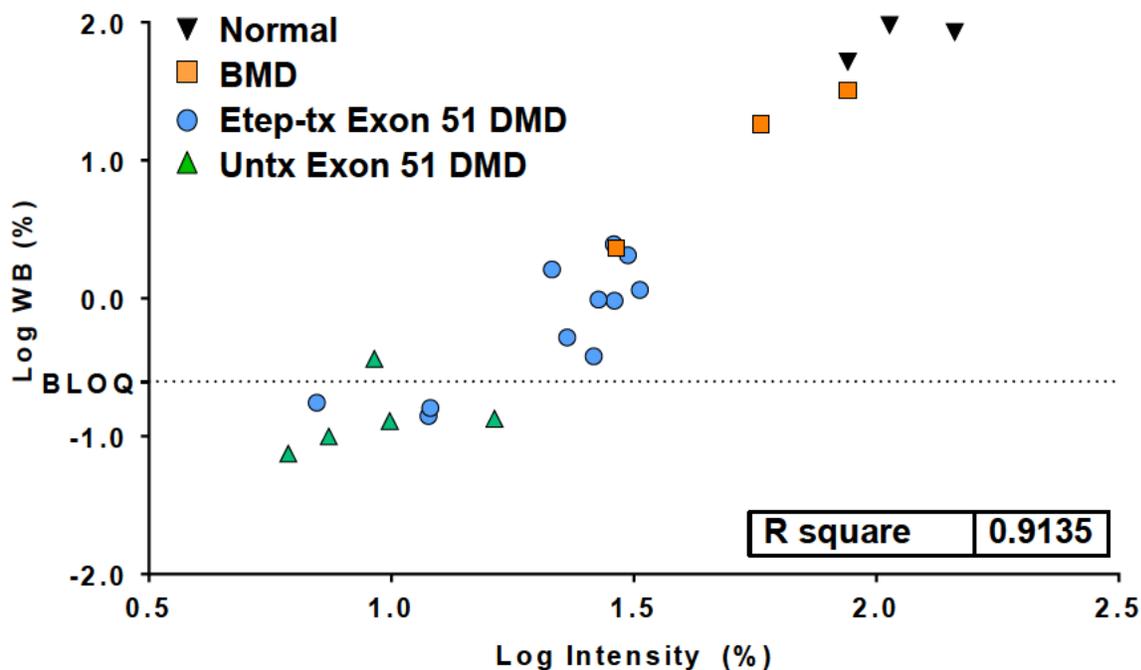
illustrated in Figure 33. Evaluating the relationship between Western Blot and IHC intensity shows that normal controls have the highest dystrophin values and untreated DMD samples have the lowest dystrophin values. Eteplirsen treated Week 180 dystrophin and BMD samples fall in between and of note, one of the low dystrophin expressing BMD patients overlaps with eteplirsen week 180 treatment samples.

The sustained production of novel dystrophin at Week 180 can only be attributed to drug treatment, providing strong and direct support for eteplirsen’s mechanism of action.

Table 22: Summary of Week 180, Studies 201/202 Dystrophin Data in Eteplirsen Treated Patients and Untreated DMD Controls

| Week 180 Dystrophin Assays | Untreated (Mean % Dystrophin of Normal) | Treated (Mean % Dystrophin of Normal) | Difference of Means (Treated vs. Untreated) | P-Value | Fold Increase |
|----------------------------|---|---------------------------------------|---|---------|---------------|
| IHC: PDPF | 1.12% | 17.39% | +16.27% | <0.001 | 15.5 |
| IHC: Intensity | 9.41% | 22.61% | +13.20% | <0.001 | 2.4 |
| Western Blot | 0.08% | 0.93% | +0.85% | 0.007 | 11.6 |

Figure 33: Positive Correlation between Dystrophin Level as Measured by Western Blot and % Relative Fiber Intensity (BIOQUANT)



7.2.6. Comparative Dystrophin Levels in DMD and BMD

There is a wide body of literature reporting on dystrophin levels in DMD and BMD. While an extensive amount of academic work has sought to identify a dystrophin threshold indicative of disease severity, 25 years of research has failed to do so. Additionally, studies have failed to find a linear relationship between dystrophin levels and muscle strength or age at different disease milestones (Hoffman 1988; Bushby 1993b; Bushby 1992; Taylor 2012; Nicholson 1993; Hoffman 1989; Anthony 2014a; van den Bergen 2014; Goldberg 1998; Lenk 1996). However what has been established is that even small amounts of dystrophin can result in a milder disease course. A clinical example for the presence of low levels of dystrophin in DMD patients resulting in a milder disease course is demonstrated by patients with mutations amenable to skipping of exon 44. Multiple studies have shown that in this population of DMD patients, trace levels of dystrophin are observed (Anthony 2014a, Bello 2016) along with a 2-year delay of median loss of ambulation (Bello 2016), mean baseline 6MWT above that of patients with other deletions (Pane 2014a) and a slower rate of decline on NSAA (Ricotti 2015). Therefore, rather than hypothesizing a numerical threshold for dystrophin levels, the DMD literature demonstrates that the most relevant therapeutic assessment is an increase in dystrophin above untreated DMD baseline.

In summary, the data presented here demonstrate an unequivocal increase in *de novo* dystrophin production following treatment with eteplirsen, providing strong and direct support for eteplirsen's mechanism of action.

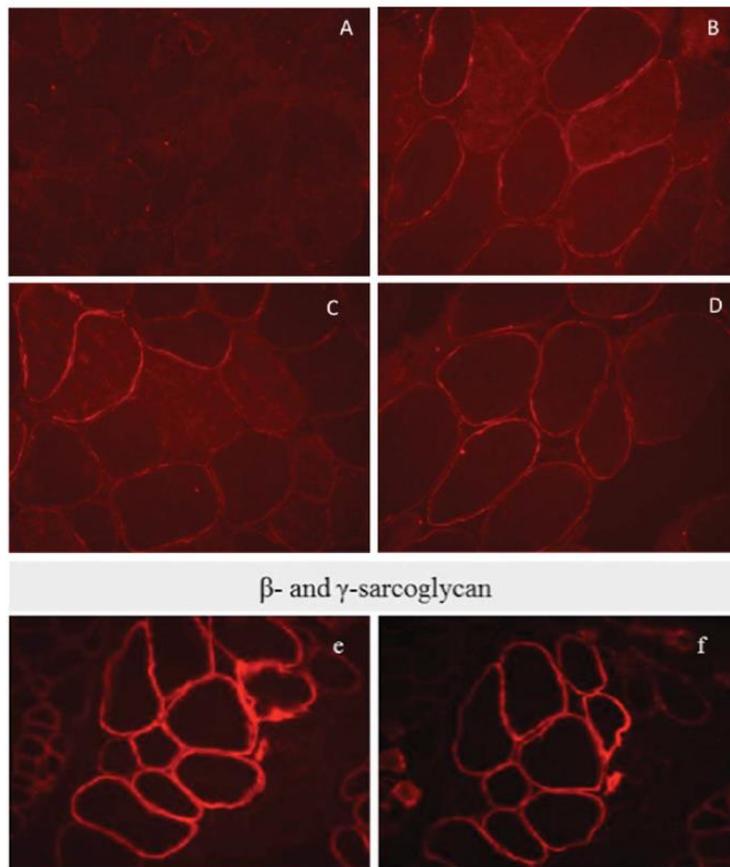
7.2.7. Cellular Localization of Dystrophin, nNOS, and Sarcoglycan Complex Proteins

The functionality of the dystrophin produced by eteplirsen is supported by IHC analysis showing localization of dystrophin with other components of the DAPC, including nitric oxide synthase (nNOS), and α -, β -, and γ -sarcoglycan, at the sarcolemma membrane. The restoration of nNOS to the membrane is especially notable as it is consistently absent in DMD muscle tissue lacking dystrophin.

Figure 34 shows muscle tissue taken from an untreated DMD patient (Panel A), a single DMD patient (Patient 006) after 48 weeks of treatment with eteplirsen in Studies 201/202 (Panels B/D), and normal healthy muscle (Panel C) and stained for nNOS. While no evidence of nNOS binding is evident in muscle taken from the untreated DMD patient (Panel A), there is clear evidence of nNOS staining in both the healthy control tissue (Panel C) and in tissue obtained from the patient treated with eteplirsen for 48 weeks (B and D). Muscle tissue from the same eteplirsen-treated patient (006) positively stained for β -Sarcoglycan (Panel E) and γ -Sarcoglycan (Panel F) confirm restoration of the DAPC complex in this patient.

Similar results, were obtained in Studies 28 and 33 (as published in Cirak 2011 and Cirak 2012).

Figure 34: Positive Staining for nNOS and Sarcoglycan Complex Proteins in an Eteplirsen-Treated Patient in Studies 201/202



Source: [Mendell 2013](#).

8. ONGOING AND PLANNED STUDIES

8.1. Ongoing Studies Supportive of Safety

Sarepta is also conducting 2 additional studies to further evaluate the safety and efficacy of eteplirsen in younger boys and boys with advanced DMD. Study 203 is an ongoing, 96-week, open-label study to evaluate the safety, efficacy, and tolerability of eteplirsen in DMD patients 4 to 6 years of age; this study includes an untreated control group of DMD patients not amenable to exon 51 skipping. Study 204 is an ongoing, 96-week, open label study of eteplirsen in non-ambulatory patients or unable to walk ≥ 300 meters on the 6MWT.

Efficacy data are not yet available for these studies; however, as of 14 August 2015 (cutoff date for the 120-Day Safety Update) safety data were available for 4 and 24 patients in Studies 203 and 204, respectively. Key aspects of these studies are summarized below.

Table 23: Ongoing Supportive Studies 203 and 204

| | Study Number | |
|-----------------------------|---|--|
| | Study 203 | Study 204 |
| Study Design | Multi-center, open-label study (US) | Multi-center, open-label study (US) |
| Dosing Regimen | Eteplirsen 30 mg/kg/week (IV) Includes untreated concurrent control group of DMD patients not amenable to exon 51 skipping | Eteplirsen 30 mg/kg/week (IV) |
| Endpoints | Primary =Safety and tolerability; Secondary =Change from BL to Wk 48 and Wk 96 in PDPF Exploratory =Dystrophin intensity; Dystrophin protein levels (Western blot); exon 51 skipping (RT PCR); T-cell infiltration; Change from BL to Wk 96 for NSAA, Time to walk 100 meters; PODCI; PK | Primary =Safety and tolerability; Exploratory =Change from BL to Wk 96 in PFTs, PUL Scale, Brooke Score for Arms and Shoulders, 9-hole peg test, ACTIVE, 10-Meter Walk/Run Test, and EK Scale |
| Required Age at Entry (yrs) | 4-6 | 7-21 |
| Study Status | Ongoing | Ongoing |
| No. Enrolled | 4 | 24 |
| No. Completed | NA | NA |
| Study Period | June 2014 –14 Aug 2015 ^a | Nov 2014 –14 Aug 2015 ^a |
| Planned Study Duration | 96 weeks | 96 weeks |

Abbreviations: ACTIVE = Ability Captured Through Interactive Video Evaluation; BL = Baseline; EK = Egen Klassifikation; IV = intravenous; NSAA = North Star Ambulatory Assessment; PDPF = percent dystrophin positive fibers; PK = pharmacokinetics; PFT = pulmonary function testing; PODCI = Pediatric Outcomes Data Collection Instrument; PUL = Performance Upper Limb Scale; RT-PCR = reverse transcriptase-polymerase chain reaction; US = United States; Wk = week.

^a Cut-off date for 120 Day Safety Update

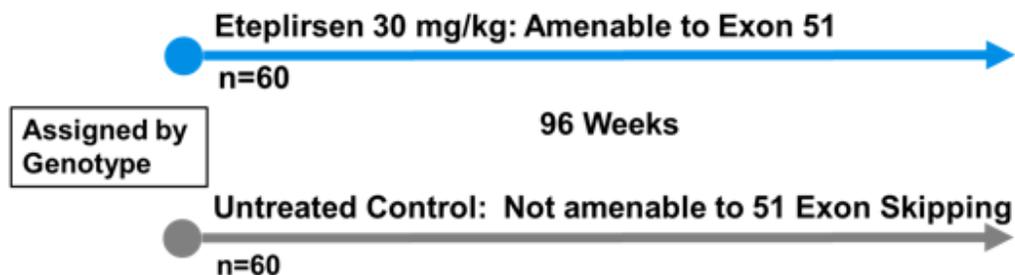
8.2. Confirmatory Studies to Support Accelerated Approval

Sarepta will conduct 2 confirmatory studies in accordance with the requirements for Accelerated Approval. Study 4658-301 (also referred to as PROMOVI) will confirm the efficacy of eteplirsen in a population of boys with DMD that is amenable to exon 51 skipping. The second study, 4045-301 (also referred to as ESSENCE) will confirm the efficacy of the PMO platform testing the efficacy of 2 other PMOs in a population of boys that is amenable to exon 45 or 53 skipping.

PROMOVI is an ongoing 96-week, open-label study evaluating the effects of eteplirsen in DMD patients amenable to exon 51 skipping in boys 7 to 16 years of age. This study will assign patients with DMD amendable to exon 51 to the eteplirsen treatment group and includes an

untreated control group of DMD patients with deletion mutations amenable to skipping exons other than 51 (Figure 35).

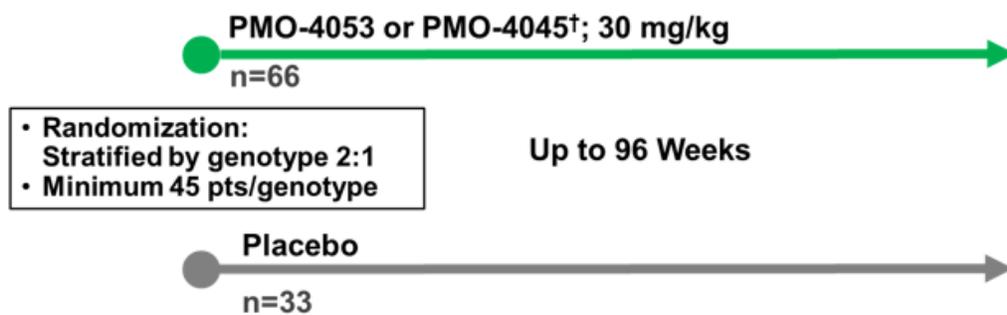
Figure 35: Study Schematic for PROMOVI



| | |
|-----------------------------|------------------------------------|
| Age (years) | 7-16 |
| 6MWT (m) | 300-450 |
| 1° Clinical Endpoint | 6MWT |
| Additional Endpoints | LOA, PFTs, NSAA, dystrophin |
| Enrollment Status | Underway |

ESSENCE is a planned, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 other PMOs, SRP-4045 and SRP-4053, in DMD patients amenable to exon 45 and 53 skipping, respectively. Both PMOs have the same chemical backbone as eteplirsen and utilize the same mechanism of action but, rather than skipping exon 51, these drugs skip exons 45 and 53, respectively.

Figure 36: Study Schematic for ESSENCE



| | |
|----------------------|------------------------------------|
| Age (years) | 7-16 |
| 6MWT (m) | 300-450 |
| Mutation | Amenable to exon 45 or 53 Skipping |
| 1° Clinical Endpoint | 6MWT |
| Additional Endpoints | LOA, PFTs, NSAA, dystrophin |

[†]PMOs have same backbone chemistry; target different DMD nucleotide sequence.

Efficacy data are not yet available for these studies; however, as of 14 August 2015 (cutoff date for the 120-Day Safety Update) safety data were available for 48 patients from Study 4658-301 (PROMOVI). Key aspects of the confirmatory studies are summarized below in [Table 24](#).

Table 24: Confirmatory Studies: 4658-301 (PROMOVI) and 4045-301 (ESSENCE)

| | Study Number | |
|-----------------------------|--|--|
| | 4658-301 PROMOVI | 4045-301 ESSENCE |
| Study Design | Multi-center, treatment assigned open-label study of eteplirsen in DMD patients amenable to skipping exon 51 (US) compared to an untreated control group of DMD not amenable to skipping exon 51 | Multi-center, randomized double-blind, placebo-controlled study of PMOs for DMD patients amenable to skipping exon 45 or 53 (US) Ratio of 2:1 |
| Dosing Regimen | Eteplirsen 30 mg/kg/week (IV) Includes untreated concurrent control group of DMD patients not amenable to exon 51 skipping | SRP-4045, SRP-4053 (according to genetic mutation) or placebo (IV) |
| Endpoints | Primary Efficacy =Change from BL 6MWT Additional Endpoints: LOA, NSAA, PFT and Dystrophin | Primary Efficacy =Change from BL 6MWT Additional Endpoints: LOA, NSAA, PFT and Dystrophin |
| Required Age at Entry (yrs) | 7-16 | 7-16 |
| Study Status | Ongoing | Planned |
| No. Planned Enrolled | 60:60 | 66:33 |

Abbreviations: 6MWT = 6 Minute Walk Test; BL = Baseline; IV = intravenous; PDPF = percent dystrophin positive fibers; PFT = pulmonary function testing; US = United States; Wk = week.

^a Cut-off date for 120-Day Safety Update.

9. SAFETY EVALUATION

9.1. Methods for Assessing Safety

Across the 7 clinical studies providing safety data, the safety and tolerability of eteplirsen were evaluated using standard safety assessments including review of adverse events (AEs), serious adverse events (SAEs), study or treatment discontinuations; safety laboratory tests (serum chemistry, hematology and coagulation, and urinalysis); electrocardiograms (ECGs); vital signs; and physical examination findings. In addition, echocardiography (ECHO) was performed to further evaluate the clinical course of cardiomyopathy associated with the underlying disease (Spurney 2014). In Studies 201/202, 204, 203 and 301, renal function was closely monitored via serial testing of blood urea, blood creatinine, urine protein, as well as serum cystatin C, due to nonclinical renal findings in kidneys (Section 4.2.2).

9.2. Safety Population

The safety population includes all patients who were randomized / enrolled and received at least 1 dose of study drug (placebo or eteplirsen) or, for untreated control patients from Study 301, all patients who had completed the Week 1 visit. The eteplirsen-treated safety population is shown in Table 25. Eteplirsen is proposed for accelerated approval for the treatment of DMD patients with mutations that are amenable to exon 51 skipping at a dose of 30 mg/kg administered by weekly IV infusion. The safety database provides data from 114 patients from 4-19 years of age at study entry, including 88 patients treated with eteplirsen 30 mg/kg or higher by weekly IV infusion. Twelve (12) patients were treated for up to 208 weeks in Studies 201/202 and 76 patients were treated with eteplirsen 30 mg/kg/wk in Studies 203, 204, and 301 for up to 40 weeks. Although the safety database is not extensive, DMD is a rare disease and the intended patient population is a discrete subpopulation that represents approximately 13% of DMD patients (Aartsma-Rus 2009) which consists of a total of 1,300 to 1,900 patients in the US. As such, the eteplirsen safety database represents approximately 6-9% of the intended US patient population for eteplirsen.

Table 25: Studies Comprising the Eteplirsen Safety Database

| Study and Description | Dose (mg/kg) | Route of Administration | Duration of Dosing (weeks) | N |
|---|----------------------|-------------------------|----------------------------|------------|
| Study 33 ^a (<i>proof of concept</i>) | 0.09, 0.9 | IM | Single dose | 7 |
| Study 28 (<i>dose ranging</i>) | 0.5, 1, 2, 4, 10, 20 | IV | 12 | 19 |
| Studies 201/202 (<i>placebo-controlled / open-label</i>) | 30, 50 | IV | 184-208 | 12 |
| Studies 301 (<i>confirmatory</i>), 204 (<i>advanced DMD</i>), and 203 (<i>younger patients</i>) | 30 | IV | 1-40 | 76 |
| All eteplirsen-treated patients | | | | 114 |

IM = single intramuscular dose; IV = once weekly intravenous infusion.

^a A single intramuscular dose was administered in Study 33.

9.3. Statistical Analysis

Descriptive statistics were used to summarize the safety data. For the purposes of the integrated safety analyses, treatment-emergent adverse events (TEAEs) were defined as any adverse event that began after the start of the first infusion (or injection) of study drug (eteplirsen or placebo) and within (\leq) 28 days after the last dose of study medication. Events with missing start dates were considered treatment emergent.

9.4. Exposure to Eteplirsen

A total of 88 patients have received once weekly eteplirsen IV at the proposed clinical dose of 30 mg/kg or higher. Of these, 61 have been treated for ≥ 12 weeks. Six patients each at 30 and 50 mg/kg eteplirsen have been treated over 4 years (Table 26).

Mean exposure for patients treated at 30 mg/kg/wk (N = 82) and 50 mg/kg/wk (N = 6) IV is 213.7 and 1394.8 days, respectively. Twelve (12) patients received eteplirsen 30 mg/kg or 50 mg/kg for approximately 4 years in Study 201/202.

Exposure to placebo for the 4 patients who received once weekly IV infusions of placebo for the first 24 weeks of Study 201 was a mean of 162.3 days. Any comparison of adverse event rates between study dose and placebo must take the variation of exposure into account.

Table 26: Extent of Exposure to Study Drug: Integrated Analyses (Safety Population)

| | Eteplirsen | | | | |
|----------------------------|--------------------|----------------------------|---------------------------|-----------------------------|--------------------------------|
| | Placebo (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Days on Study Drug | | | | | |
| N | 4 | 82 | 6 | 107 | 114 |
| Mean | 162.3 | 213.7 | 1394.8 | 255.4 | 239.8 |
| SD | 1.26 | 342.29 | 87.03 | 412.93 | 404.62 |
| Median | 162.0 | 126.5 | 1449.5 | 97.0 | 89.5 |
| Min, Max | 161, 164 | 1, 1451 | 1282, 1453 | 1, 1453 | 1, 1453 |
| Eteplirsen exposure | | | | | |
| | Route | Dose | | Patients Exposed (N) | |
| ≥ 1 dose | IM or IV | any | | 114 | |
| ≥ 1 dose | IV | any | | 107 | |
| ≥ 1 dose | IV | ≥ 30 mg/kg | | 88 | |
| ≥ 3 months | IV | ≥ 30 mg/kg | | 61 | |
| ≥ 6 months | IV | ≥ 30 mg/kg | | 36 | |
| ≥ 4 years | IV | ≥ 30 mg/kg | | 12 | |

Abbreviations: IM = intramuscular; IV = intravenous; max = maximum; min = minimum; SD = standard deviation.

9.5. Treatment-emergent Adverse Events

9.5.1. General Overview of Adverse Events

The majority of patients in each treatment group, including placebo, experienced at least 1 TEAE. TEAEs were reported for 88 (82.2%) patients in the ‘eteplirsen IV’ group (i.e., all patients receiving eteplirsen IV at any dose, N = 107), and 63 (76.8%) patients in the 30 mg/kg IV group (N = 82).

No deaths or life-threatening events occurred during the eteplirsen clinical studies (see [Section 9.5.4](#)). Two (2) patients experienced a treatment-emergent SAE; none of the SAEs were considered related to treatment. One (1) patient discontinued treatment with eteplirsen due to a TEAE ([Section 9.5.5](#)).

Five (5) patients (4.7%) in the ‘eteplirsen IV’ group (3 of whom received 30 mg/kg IV) and 1 patient in the untreated group experienced severe TEAEs ([Section 9.5.6](#)). TEAEs that were considered related to study drug occurred in 35 (32.7%) patients in the ‘eteplirsen IV’ group, 18 (22.0%) patients in the 30 mg/kg group, and in 1 patient (25.0%) in the placebo group ([Section 9.5.7](#)).

The limited numbers of adverse events that were severe, serious, or resulted in discontinuation were observed across dose groups with no suggestion of a dose effect.

9.5.2. Adverse Events in the Placebo-Controlled Period of Study 201

Safety data in patients who received 30 or 50 mg/kg/wk eteplirsen or placebo (N = 4 per group) over a 24-week period are available from Study 201.

All patients experienced at least 1 TEAE during the 24-week placebo-controlled period of the study. Review of all TEAEs by system organ class (SOC) did not show any increases in the frequency of events within any SOC in eteplirsen-treated patients versus placebo-treated patients or with increasing dose of eteplirsen.

There were 19 TEAEs that occurred in ≥ 2 patients as presented below in [Table 27](#). A table of all TEAEs occurring in the placebo-controlled period of Study 201 is provided in [Appendix 16](#).

Table 27: Treatment-Emergent Adverse Events Occurring in ≥ 2 Patients During the 24-Week Placebo-Controlled Period of Study 201

| System Organ Classification Preferred Term | Eteplirsen | | | |
|---|---------------------------|-------------------------------|-------------------------------|----------------------------------|
| | Placebo N = 4 n (%) | 30 mg/kg IV N = 4 n (%) | 50 mg/kg IV N = 4 n (%) | All Eteplirsen N = 8 n (%) |
| Number of Subjects With a TEAE | 4 | 4 | 4 | 8 |
| Injury, poisoning & procedural complications | | | | |
| Procedural pain | 3 (75.0%) | 1 (25.0%) | 3 (75.0%) | 4 (50.0%) |
| Fall | 1 (25.0%) | 1 (25.0%) | 0 | 1 (12.5%) |
| Incision site pain | 1 (25.0%) | 1 (25.0%) | 0 | 1 (12.5%) |
| Respiratory, thoracic & mediastinal disorders | | | | |
| Oropharyngeal pain | 3 (75.0%) | 3 (75.0%) | 0 | 3 (37.5%) |
| Cough | 2 (50.0%) | 1 (25.0%) | 1 (25.0%) | 2 (25.0%) |
| Nasal congestion | 2 (50.0%) | 1 (25.0%) | 0 | 1 (12.5%) |
| Musculoskeletal & connective tissue disorders | | | | |
| Pain in extremity | 3 (75.0%) | 0 | 1 (25.0%) | 1 (12.5%) |
| Back pain | 2 (50.0%) | 1 (25.0%) | 0 | 1 (12.5%) |
| Nervous system disorders | | | | |
| Balance disorder | 0 | 1 (25.0%) | 2 (50.0%) | 3 (37.5%) |
| Headache | 2 (50.0%) | 1 (25.0%) | 0 | 1 (12.5%) |
| General disorders & administration site conditions | | | | |
| Pyrexia | 2 (50%) | 1 (25.0%) | 0 | 1 (12.5%) |
| Metabolism & nutrition disorders | | | | |
| Hypokalaemia | 2 (50.0%) | 2 (50.0%) | 2 (50.0%) | 4 (50.0%) |
| Gastrointestinal disorders | | | | |
| Vomiting | 0 | 1 (25.0%) | 2 (50.0%) | 3 (37.5%) |
| Abdominal pain | 2 (50.0%) | 0 | 0 | 0 |
| Diarrhoea | 1 (25.0%) | 0 | 1 (25.0%) | 1 (12.5%) |
| Nausea | 1 (25.0%) | 0 | 1 (25.0%) | 1 (12.5%) |
| Infections & infestations | | | | |
| Rhinitis | 1 (25.0%) | 0 | 1 (25.0%) | 1 (12.5%) |

Table 27: Treatment-Emergent Adverse Events Occurring in ≥ 2 Patients During the 24-Week Placebo-Controlled Period of Study 201

| System Organ Classification Preferred Term | Eteplirsen | | | |
|---|---------------------------|-------------------------------|-------------------------------|----------------------------------|
| | Placebo N = 4 n (%) | 30 mg/kg IV N = 4 n (%) | 50 mg/kg IV N = 4 n (%) | All Eteplirsen N = 8 n (%) |
| Vascular disorders | | | | |
| Haematoma | 1 (25.0%) | 1 (25.0%) | 1 (25.0%) | 2 (25.0%) |
| Skin & subcutaneous tissue disorders | | | | |
| Dermatitis contact | 0 | 2 (50.0%) | 0 | 2 (25.0%) |

Abbreviations: IV = intravenous; TEAE = treatment-emergent adverse event.

Note: Patients were counted once in each body system and preferred term.

9.5.3. Adverse Events in the Integrated Safety Analysis

Common adverse events, defined as TEAEs reported in $\geq 10\%$ of all eteplirsen-treated patients, are summarized in [Table 28](#) and all adverse events that occurred in eteplirsen-treated patients are summarized in [Appendix 17](#).

The most commonly experienced TEAEs were consistent with the underlying diagnosis of DMD, steroid treatment, and/or the pediatric nature of the patient population and included headache (27 patients; 23.7%); back pain and vomiting (24 patients each; 21.1%); cough (18 patients, 15.8%); pain in extremity (17 patients; 14.9%); procedural pain (16 patients; 14.0%); upper respiratory infection (15 patients; 13.2% each); arthralgia, contusion, excoriation, oropharyngeal pain, and nasopharyngitis (14 patients each, 12.3%); and nasal congestion (13 patients; 11.4%). Of these, the following occurred more frequently in patients who received 30 or 50 mg/kg eteplirsen IV than in patients who received placebo: headache, vomiting, cough, procedural pain, upper respiratory tract infection, arthralgia, contusion, excoriation, nasopharyngitis and nasal congestion, however this needs to be interpreted in the context of the shorter exposure period for placebo treated patients. The majority of these common TEAEs were mild in severity, considered not related to study drug, and resolved during continued treatment with study drug.

Table 28: Treatment-Emergent Adverse Events Observed in ≥10% of ‘All Eteplirsen’ Patients by System Organ Classification and Preferred Term: Integrated Analyses (Safety Population)

| System Organ Classification Preferred Term | Placebo (N = 4) | 0.09 & 0.9 mg IM (N = 7) | Eteplirsen | | | | | | |
|---|-----------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Number of Patients With a TEAE Occurring in ≥10% of Patients While on Eteplirsen | 4 (100%) | 0 | 11 (100%) | 3 (75.0%) | 2 (50.0%) | 47 (57.3%) | 6 (100%) | 69 (64.5%) | 69 (60.5%) |
| Musculoskeletal and connective tissue disorders | | | | | | | | | |
| Back pain | 2 (50.0%) | 0 | 3 (27.3%) | 1 (25.0%) | 0 | 17 (20.7%) | 3 (50.0%) | 24 (22.4%) | 24 (21.1%) |
| Pain in extremity | 3 (75.0%) | 0 | 2 (18.2%) | 1 (25.0%) | 0 | 10 (12.2%) | 4 (66.7%) | 17 (15.9%) | 17 (14.9%) |
| Arthralgia | 0 | 0 | 3 (27.3%) | 0 | 0 | 8 (9.8%) | 3 (50.0%) | 14 (13.1%) | 14 (12.3%) |
| Injury, poisoning and procedural complications | | | | | | | | | |
| Procedural pain | 3 (75.0%) | 0 | 2 (18.2%) | 0 | 0 | 8 (9.8%) | 6 (100%) | 16 (15.0%) | 16 (14.0%) |
| Contusion | 0 | 0 | 1 (9.1%) | 0 | 0 | 10 (12.2%) | 3 (50.0%) | 14 (13.1%) | 14 (12.3%) |
| Excoriation | 0 | 0 | 0 | 0 | 1 (25.0%) | 11 (13.4%) | 2 (33.3%) | 14 (13.1%) | 14 (12.3%) |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | | |
| Cough | 2 (50.0%) | 0 | 2 (18.2%) | 0 | 0 | 12 (14.6%) | 4 (66.7%) | 18 (16.8%) | 18 (15.8%) |
| Oropharyngeal pain | 3 (75.0%) | 0 | 0 | 0 | 0 | 10 (12.2%) | 4 (66.7%) | 14 (13.1%) | 14 (12.3%) |
| Nasal congestion | 1 (25.0%) | 0 | 0 | 0 | 0 | 11 (13.4%) | 2 (33.3%) | 13 (12.1%) | 13 (11.4%) |
| Nervous system disorders | | | | | | | | | |
| Headache | 2 (50.0%) | 0 | 5 (45.5%) | 2 (50.0%) | 1 (25.0%) | 14 (17.1%) | 5 (83.3%) | 27 (25.2%) | 27 (23.7%) |
| Gastrointestinal disorders | | | | | | | | | |
| Vomiting | 0 | 0 | 2 (18.2%) | 1 (25.0%) | 0 | 18 (22.0%) | 3 (50.0%) | 24 (22.4%) | 24 (21.1%) |

Table 28: Treatment-Emergent Adverse Events Observed in $\geq 10\%$ of ‘All Eteplirsen’ Patients by System Organ Classification and Preferred Term: Integrated Analyses (Safety Population)

| System Organ Classification Preferred Term | Placebo (N = 4) | 0.09 & 0.9 mg IM (N = 7) | Eteplirsen | | | | | | |
|---|--------------------|--------------------------------|----------------------------------|---------------------------|---------------------------|----------------------------|---------------------------|------------------------|--------------------------------|
| | | | ≤ 4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Infections and infestations | | | | | | | | | |
| Upper respiratory tract infection | 0 | 0 | 3 (27.3%) | 2 (50.0%) | 1 (25.0%) | 5 (6.1%) | 4 (66.7%) | 15 (14.0%) | 15 (13.2%) |
| Nasopharyngitis | 1 (25.0%) | 0 | 0 | 0 | 0 | 10 (12.2%) | 4 (66.7%) | 14 (13.1%) | 14 (12.3%) |

Abbreviations: IM = intramuscular; IV = intravenous; TEAE = treatment-emergent adverse event.

Note: AEs are coded using MedDRA V14.0. AEs were attributed to the treatment being received at start of AE. TEAEs are those starting during or after the first infusion of study drug (or week 1 for untreated patients) or within 28 days after the last infusion (or last visit for untreated patients). Patients who experience a coded event more than once are only counted once per treatment received

9.5.4. Deaths and Other Serious Adverse Events

There have been no deaths and no life-threatening SAEs with an overall exposure of 72 patient years.

Two (2) treatment-emergent SAEs (one event each of moderate vomiting and severe femur fracture) have been reported in the eteplirsen clinical development program. These were considered as unrelated to study drug. A brief narrative summary for each of these is provided below.

In addition, 4 SAEs that did not occur on eteplirsen have also been reported: 1 ‘treatment emergent’ event that occurred in an untreated patient in Study 301 (lymphadenitis viral); 2 events (ankle fracture, wound infection) that occurred more than 28 days after the patient had discontinued study medication; and 1 event (postoperative oxygen saturation decreased due to emesis) that occurred prior to treatment in a post-operative setting.

Patient 201/202-01-009 (eteplirsen 30 mg/kg)

Femur Fracture (fracture of right distal femur)

Severe, unrelated

Patient 201/202-01-009 was a 9-year-old boy with DMD enrolled in Studies 201/202 in the 30 mg/kg IV group. On (b) (6) (Study Day 608), he sustained a fracture of the right distal femur after falling out of his wheelchair when his mother made a sudden stop in their van. He had taken off his seatbelt. He was taken to the emergency room where an X-ray confirmed he had suffered a closed stable femoral fracture; a cast was applied. He received versed, opioids, fentanyl, and ibuprofen for pain relief. Approximately 2 months later, the patient recovered from this event.

Patient 28-01-107 (eteplirsen 2 mg/kg)

Vomiting (post-operative nausea and vomiting)

Moderate, Unrelated

Patient 28-01-107 was a 10-year-old boy diagnosed with DMD and enrolled in Study 28. He received 12 doses of once weekly eteplirsen 2.0 mg/kg IV beginning on 02 July 2009.

On (b) (6), 12 days after the last dose of study drug, he was admitted to the hospital for the protocol-specified muscle biopsy to be performed under general anesthesia. Per standard procedure prior to general anaesthesia, the patient fasted the night before surgery. Initially following the procedure, he made a good recovery and was given liquid and a light diet that evening; however, later that evening (at approximately 20:00 hours), he developed nausea and vomiting. On physical examination, his vital signs were normal and he looked well. Laboratory results from that day were consistent with his underlying DMD condition and were considered unremarkable. His sodium, chloride, and potassium levels were within the normal range. The following day ((b) (6)), the event of vomiting was considered resolved and he was discharged. The Investigator attributed the event to the prolonged fasting (12 hours) prior to general anesthesia.

9.5.5. Adverse Events Leading to Drug or Study Discontinuation

One (1) patient, a 10-year-old boy with DMD enrolled in Study 28, discontinued treatment due to a TEAE (cardiomyopathy).

Patient 28-02-202 (eteplirsen 4 mg/kg)

*Cardiomyopathy (Cardiomyopathy [left ventricular dysfunction])
Severe, Possibly related*

Patient 28-02-202, a 10-year-old boy in the 4 mg/kg IV dose group, had 3 reported TEAEs of mild tachycardia and 1 TEAE of sinus tachycardia on Days 1, 8, 24 and 36, with heart rate up to 127 beats per minute. An echocardiogram was performed and revealed decreased fractional shortening of 22% (ejection fraction [EF] of 40% to 45%). The investigator reported this finding as an adverse event of cardiomyopathy (described as ‘cardiomyopathy [left ventricular dysfunction]’) that was possibly related to eteplirsen and led to study drug discontinuation on Day 47 (after 7 doses of eteplirsen 4 mg/kg IV). Retrospective review of echocardiograms obtained prior to study entry showed evidence for pre-existing cardiomyopathy per the investigator’s report. Moreover, subsequent re-evaluation of all study echocardiograms of this patient by an independent cardiologist (without the cardiologist being provided clinical details of the adverse event) determined normal left ventricular ejection fraction (>55%) on all study echocardiograms.

Given the possibility of presence of left ventricular dysfunction prior to study treatment, and inconsistency with respect to independent interpretation of the echocardiographic data, a relationship between study drug and this event is difficult to establish. Further discussion of cardiac function, including the diagnosis and prevalence of cardiomyopathy in the DMD population, is provided in the section on adverse events of special interest ([Section 9.5.8.1](#)).

9.5.6. Severe Adverse Events

The majority of TEAEs across all treatment groups were mild or moderate in intensity, as assessed by the Investigator. A total of 5 eteplirsen-treated patients (4.4%) experienced 8 severe TEAEs, including incision site haemorrhage, haemorrhoids, back pain, cardiomyopathy, nasal congestion, balance disorder, bone pain, and femur fracture. With the exception of cardiomyopathy ([Section 9.5.5](#)), which was considered by the investigator to be possibly related to treatment, all other severe events were considered unrelated to study drug. In addition, one untreated patient experienced one event of lymphadenitis viral that was considered severe in intensity and that met the criteria for seriousness.

9.5.7. Treatment-Related Adverse Events

TEAEs assessed by the investigator to be possibly, probably, or definitely related to study treatment were considered treatment-related. Overall, treatment-related TEAEs were reported in 36 (31.6%) patients in the ‘all eteplirsen’ treatment group and in 1 (25%) patient in the placebo group. In the ‘all eteplirsen’ group, the most frequent treatment-related TEAEs were headache (8 patients, 7.0%), proteinuria (4 patients, 3.5%), and dizziness, fatigue, vomiting, and tachycardia (each in 3 patients, 2.6%). One (1) patient was reported to have a treatment-related TEAE of nausea while receiving placebo. Treatment-related TEAEs occurred across dose groups with no indication of a dose effect.

Treatment-related TEAEs were reported in 21 (23.9%) of the 88 patients who received eteplirsen at either 30 or 50 mg/kg IV weekly, the treatment groups that represent the greatest exposure to eteplirsen. Of these, proteinuria, protein urine present, thrombosis in device, vomiting, and flushing were reported in >1 patient; these TEAEs are discussed in more detail in [Section 9.5.8](#), Adverse Events of Special Interest.

9.5.8. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for the eteplirsen program included potential safety related findings based on manifestations of the underlying DMD disease (cardiac function), nonclinical observations with eteplirsen (renal function, see [Section 9.5.8.2](#)), AEs associated with other RNA analogs (renal and hepatic function, coagulopathy and infusion site reactions), and general precautions with administration of a compound in clinical development (infusion related reactions, hypersensitivity, severe cutaneous reactions, leukopenia and neutropenia).

The inclusion of adverse events associated with other RNA analogs in Adverse Events of Special Interest for eteplirsen, a phosphorodiamidate morpholino oligomer, is a conservative approach, since the non-clinical toxicity data for eteplirsen did not show a signal except for renal findings at the highest dose administered ([Section 4.2.2](#)). Other RNA analogs, specifically phosphorothioate oligonucleotide therapeutics have been associated with renal toxicity, including increases in proteinuria, $\alpha 1$ microglobulin, and KIM 1 ([McGowan 2012](#); [Goemans 2011](#)); elevated levels of transaminases and hepatic steatosis ([McGowan 2012](#)); thrombocytopenia and other coagulation related adverse events ([Goemans 2014](#)); and injection site reactions ([Voit 2014](#), [McGowan 2012](#)).

To identify potential AESIs, search criteria for specific MedDRA preferred terms were developed. In addition, medical review of all TEAEs, as well as relevant laboratory, vital sign, ECG and echocardiogram results was performed.

9.5.8.1. Cardiac Function

In addition to progressive muscle weakness and wasting, manifestations of DMD typically include cardiac symptoms. While cardiac function is generally normal during early childhood, they progressively worsen over time, and patients typically die from cardiac or respiratory failure ([Brooke 1989](#); [Eagle 2002](#)).

Boys with DMD have a resting heart rate that is consistently higher than normal even when cardiac function remains normal. Although elevation in resting heart rate in this patient population is likely multifactorial, it is associated with increased risk of cardiomyopathy ([Thomas 2012](#)), which is usually diagnosed after the age of 10 years as dilated cardiomyopathy with reduced left ventricular ejection fraction in boys with DMD. While cardiomyopathy rarely manifests clinically in the early teens in DMD patients, the prevalence of cardiomyopathy as measured by a left ventricular ejection fraction of <55% has been estimated at 27% overall. Cardiomyopathy shows an increasing prevalence with age and disease progression, with 10% to 20% of patients affected between 6 and 13 years of age and over 60% of patients ≥ 18 years affected ([Spurney 2014](#)). A long latency between initial abnormal cardiac findings in laboratory assessments and clinically manifest cardiomyopathy exists, and the pathology includes myocyte atrophy, hypertrophy and fibrosis.

In the ‘all eteplirsen’ group, 6 patients (5.3%) had a total of 12 reported events potentially indicative of a cardiac disorder. None of the events was serious, and the majority of events were assessed by the investigator as mild in intensity (9/12) and as possibly related (7/12) to eteplirsen (Table 29).

The observed TEAEs included cardiomyopathy, congestive cardiomyopathy, cardiac fibrosis, tachycardia, and sinus tachycardia, and were distributed across dose groups with no suggestion of a dose effect. One (1) 10-year-old patient (28-02-202) with mild events of tachycardia and sinus tachycardia prematurely discontinued treatment in Study 28 due to an event of cardiomyopathy; this event was described above in Section 9.5.5. The other event of cardiomyopathy was reported in a 13-year-old patient 27 days after a single low dose of eteplirsen 0.09 mg IM. An event of cardiac fibrosis was identified by routine cardiac MRI as part of DMD natural history surveillance at the study site and was considered to be related to the underlying disease of DMD:

Patient 204-206-104 (eteplirsen 30 mg/kg)

Cardiac fibrosis

Mild, not related

Patient 204-206-104 was a 14-year-old with advanced DMD who experienced mild, asymptomatic cardiac fibrosis on Day 120, after receiving 18 eteplirsen doses. The finding was identified by routine cardiac MRI as part of DMD natural history surveillance at the study site. The event is ongoing and the patient remains asymptomatic. The Investigator assessed causality of the event as unrelated to study drug or study procedures, and definitely related to the underlying disease of DMD. The patient’s cardiologist started him on spironolactone. No action was taken with study drug administration and the patient remained in the study through the D120 data cutoff.

Table 29: Cardiac Function TEAEs

| Patient ID | Age (yr) | Dose (mg/kg) | Preferred Term | Treatment Related | Severity | Outcome |
|----------------|----------|-------------------|---------------------------|-------------------|----------|---------------|
| 204-206-104 | 14 | 30 | Cardiac fibrosis | No | Mild | Not recovered |
| 201/202-01-006 | 10 | 30 | Tachycardia | No | Moderate | Not recovered |
| | | | Tachycardia (worsening) | No | Moderate | Recovered |
| | | | Tachycardia | No | Mild | Recovered |
| 28-02-205 | 10 | 20 | Tachycardia | Possibly | Mild | Not recovered |
| 28-02-207 | 9 | 20 | Tachycardia | Possibly | Mild | Not recovered |
| 28-02-202 | 10 | 4 | Cardiomyopathy | Possibly | Severe | Not recovered |
| | | | Sinus tachycardia × 3 | Possibly | Mild | Recovered |
| | | | Tachycardia | Possibly | Mild | Recovered |
| 33-01-002 | 13 | 0.09 ^a | Congestive cardiomyopathy | No | Mild | Unknown |

^a Patient 33-01-002 received a single 0.09-mg intramuscular dose of eteplirsen.

In addition, 3 patients had 5 reported events of tachycardia and sinus tachycardia.

To further evaluate the cardiac clinical course of patients with DMD, predefined criteria were established for abnormal changes for QTcF; there were no patients who met predefined criteria for QTcF. Of the predefined criteria for abnormal ECG results, only the criterion for abnormal HR (HR >120 bpm) was met. A total of 7 patients (1 in ≤4 mg/kg, 2 in 20 mg/kg, and 4 in 30 mg/kg) met this criterion; 3 of these patients had reported TEAEs of tachycardia or sinus tachycardia (Table 29). The remaining 4 patients had a single occurrence of HR >120 bpm with no reported cardiac events associated with elevated heart rate. It should be noted that 4 additional patients also experienced heart rates above 120 bpm prior to treatment initiation.

In addition, serial echocardiograms were conducted in Studies 201/202. None of the patients in the safety population had left ventricular ejection fraction results that met the criteria for a predefined abnormal change. Longitudinal analysis of the left ventricular ejection fraction as assessed at the annual milestone visits in Studies 201/202 is provided in Table 30 below. In this table, the Week 24 assessment was used as baseline in patients originally randomized to placebo to ensure that only the period on eteplirsen treatment is represented. These data characterize the stability of LVEF in patients treated with eteplirsen over 4 years.

Table 30: Left Ventricular Ejection Fraction over Time in Studies 201/202

| Timepoint | Patients Treated with Eteplirsen at 30 or 50 mg/kg IV (N = 12) | | |
|-----------|--|-------------|---------------|
| | N | Median LVEF | Min, Max LVEF |
| Baseline | 12 | 61.5 | 50, 74 |
| Year 1 | 11 | 66.0 | 52, 71 |
| Year 2 | 12 | 62.5 | 54, 67 |
| Year 3 | 12 | 65.0 | 53, 71 |
| Year 4 | 8 ¹ | 62.0 | 55, 76 |

Abbreviations: LVEF = left ventricular ejection fraction; max = maximum; min = minimum

¹ At the time of the data cut for the Day 120 Safety Update, the 4 patients initially on placebo had not been on eteplirsen treatment for 4 years.

The occurrence of tachycardia, cardiomyopathy and cardiac fibrosis observed during clinical trials with eteplirsen was not related to study dose or duration of administration, is not unexpected in the DMD population enrolled, and appears consistent with the underlying disease.

9.5.8.2. Renal Function

The primary elimination pathway for eteplirsen is renal, and the kidney was identified as the primary target organ for toxicity in nonclinical toxicology studies. In addition, other RNA analogs, specifically phosphorothioate oligonucleotides, have been associated with renal toxicity, including increases in proteinuria, α1 microglobulin, and KIM 1 (McGowan 2012; Goemans 2011).

While serum creatinine levels are typically a fairly reliable indicator of kidney function, this may not be the case in patients with more advanced DMD whose basal creatinine levels tend to be low or low normal due to decreased muscle mass (Viollet 2009). Thus, serum cystatin C may provide an alternative measure of renal function.

In the “all eteplirsen” group, 16 patients (14.0%) had a total of 21 TEAEs potentially indicative of renal events. One (1) patient in the placebo group had an event of proteinuria and one patient in the 30 mg/kg treatment group had an event of proteinuria prior to treatment initiation. None of the events were serious, and all were assessed by the investigator as mild in intensity. The majority of events were transient and spontaneously resolved with ongoing study drug administration. Nine (9) patients (7.9%) had 9 TEAEs that were reported by the investigator as treatment related (Table 31).

Table 31: Treatment-related TEAEs Potentially Indicative of Renal Toxicity

| Patient ID | Age (year) | Dose (mg/kg) | Preferred Term | Treatment Related | Severity | Outcome |
|----------------|------------|--------------|-------------------------|-------------------|----------|---------------|
| 201/202-01-004 | 8 | 50 | Hypercalciuria | Possibly | Mild | Not recovered |
| 201/202-01-015 | 9 | 50 | Proteinuria | Possibly | Mild | Recovered |
| 204-202-101 | 13 | 30 | Protein urine present | Possibly | Mild | Recovered |
| 204-202-104 | 11 | 30 | Protein urine present | Possibly | Mild | Recovered |
| 204-233-105 | 17 | 30 | Blood urine present | Possibly | Mild | Not recovered |
| 301-213-001 | 12 | 30 | Urine analysis abnormal | Possibly | Mild | Recovered |
| 301-218-004 | 9 | 30 | Proteinuria | Possibly | Mild | Recovered |
| 301-234-001 | 12 | 30 | Proteinuria | Possibly | Mild | Recovered |
| 201/202-01-006 | 10 | 30 | Proteinuria | Possibly | Mild | Recovered |

Proteinuria/urine protein present were the most common reported adverse events; these events were transient or sporadic, spontaneously resolved with ongoing treatment, and were not associated with increasing renal laboratory values, with the exception of 1 patient who had evidence of transient renal laboratory abnormalities in the setting of dehydration (Patient 201/202-01-003, 50 mg/kg IV). No other concurrent indicators of renal toxicity were reported. Only 1 event of proteinuria (Patient 204-202-101, 30 mg/kg IV) led to interruption of study drug. This patient resumed treatment after missing 1 dose without further TEAEs or abnormal laboratory findings.

Adverse Events of Proteinuria / Protein Urine Present

In the ‘all eteplirsen’ group, of the 16 patients with reported renal events, 11 patients (9.6%) had reported TEAEs of either proteinuria (10 TEAEs) or protein urine present (2 TEAEs). Of these 12 events, 6 (50.0%) were considered possibly related to treatment. In addition, 1 event of proteinuria was reported in 1 patient who was receiving placebo. All events were mild with no consistent pattern of time to onset (onset ranged from Day 1 to Day 785), and all patients continued treatment uninterrupted with 1 exception (1 dose of study medication was withheld as a precautionary measure for Patient 204-202-101).

In 10 of the 11 patients, the events were isolated with no increases in serum BUN, serum cystatin C, or urine KIM 1, had no accompanying symptoms of renal disease, were generally

mild, transient, and resolved in subsequent assessments. The case of proteinuria with associated changes in laboratory values is briefly summarized below.

Patient 201/202-01-003 (eteplirsen 50 mg/kg)

*Blood creatinine increased, Blood urea increased, Dehydration, Proteinuria
Mild, Not related*

Patient 201/202-01-003 (50 mg/kg IV), who was 7 years of age at baseline, experienced blood creatinine increased, blood urea nitrogen increased and proteinuria at Week 60, with concurrent abnormal laboratory findings of creatinine 102.5 $\mu\text{mol/L}$, blood urea nitrogen (BUN) 14.6 mmol/L, and trace urine protein at the time of the observed laboratory abnormalities. Of note, the serum cystatin C and urine KIM 1 values at the time of the TEAEs were normal. Both BUN and creatinine abnormalities had resolved by the time of re-testing 11 days later and remained normal with continued eteplirsen treatment through data cutoff at Week 208. Subsequent urinalysis was sporadically positive for trace or 1+ protein. The investigator interpreted this event in the context of dehydration, noting that this patient had a history of dehydration on several occasions, and a TEAE of dehydration was recorded. The patient remained in the study and continued to receive study drug through data cutoff at Week 208.

In addition, a value of 2+ urine protein on dipstick, corresponding to ≥ 100 mg/dL and < 300 mg/dL, was predefined as the criterion for a markedly abnormal value; 5 treated patients had a post-treatment 2+ urine protein value that was not recorded as an AE. In all cases, the finding was a single occurrence that spontaneously resolved with ongoing treatment. It should be noted that 2+ urine protein values were also recorded prior to treatment.

Additional renal TEAEs included dehydration, chromaturia, crystalluria, hypercalciuria, blood creatinine increased, blood urea increased, blood urine present, and urine analysis abnormal; with the exception of dehydration, which was reported in 2 patients, these events were reported in only 1 patient (per event).

Laboratory observations of protein in urine (Study 201/202)

To assess whether or not elevations in urine protein were increasing over time with eteplirsen, a longitudinal analysis of positive ($\geq 1+$ by dipstick, corresponding to ≥ 30 mg/dL and < 100 mg/dL) urine protein findings over time in Studies 201/202 was performed. Over the 4-year period, a total of 721 urinalysis assessments were performed in the 12 patients. Overall, 702 ($>97\%$) of the assessments were normal, and no increase in the occurrence of urine protein was observed over time, suggesting no cumulative effect (Table 32).

Table 32: Instances of Urine Protein $\geq 1+$ Over Time in Studies 201/202 (based on urinalysis by dipstick assay)

| Timepoint | Instances of protein in urine $\geq 1+$ | Number of Assessments |
|---------------------------------|---|-----------------------|
| Placebo and Prior to dosing | 2 | 68 |
| Week 0-48 | 3 | 183 |
| Week 48-96 | 6 | 150 |
| Week 96-144 | 5 | 152 |
| Week 144-Week 208 (data cutoff) | 3 | 168 |

Laboratory Observations of Serum Creatinine and Cystatin C

In patients with DMD, creatinine levels tend to be low or low normal due to decreased muscle mass. Serum cystatin C is less dependent on muscle mass and therefore, may provide a better measure of renal function. Thus, serum cystatin C levels were evaluated in the eteplirsen clinical program as an additional biomarker of kidney function.

One patient (201/202 01 003), described above, had a creatinine value that met predefined criteria for an increase over baseline of ≥ 35 $\mu\text{mol/L}$ and a clinically noteworthy treatment-emergent value. No other patient treated with eteplirsen met the criterion for abnormal change, and no other patient had a creatinine value above the ULN while on eteplirsen treatment. Patient 201/202 01 003 was discussed above.

Two (2) patients (1 in the 30 mg/kg IV dose group and 1 untreated) had a shift from normal to high for serum cystatin C. Concurrent BUN and creatinine values were normal, urine protein was negative, and cystatin C levels returned to normal at the next assessment for both patients.

Adverse events of Myoglobinuria

There were 4 AEs of myoglobinuria reported in eteplirsen studies. All of the myoglobinuria events were reported in Study 33, after a single intramuscular (IM) dose, in the 0.9mg/kg IM arm. The myoglobinuria was reported on the day that study drug was administered for 3 of the 4 subjects, and was reported on the day of the post-treatment biopsy for the remaining subject (on Day 29). The myoglobinuria events were self-limited and resolved, without treatment. Due to the temporal relationship between the administration of general anesthesia and the onset of myoglobinuria, the general anaesthesia may have contributed to the onset of these events; however, it is more likely that direct injury to muscle following the IM injection or the muscle biopsy caused the observed myoglobinuria. Myoglobinuria events were not observed in subsequent eteplirsen studies.

In summary, protein in urine was observed not only during treatment with eteplirsen, but also in patients prior to dosing. In addition, there was a lack of concurrent elevation of other markers of renal function, including BUN, creatinine, and cystatin C, (with the exception of one event of increased BUN and creatinine as described above) and spontaneous resolution was observed with ongoing eteplirsen dosing. The data suggest that protein in urine may occur in the background population. Additional renal events were isolated, mild in intensity, and the majority resolved

with ongoing treatment. Thus, the data generated to date do not suggest an association between renal dysfunction and eteplirsen at this time.

9.5.8.3. Hepatic Function

There were no treatment emergent adverse events representative of a potential drug-induced hepatotoxicity.

Laboratory Observations of Liver Function Tests

Traditional criteria to assess liver function may have limited applicability in the DMD population, because high transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] up to approximately $22 \times$ ULN) are generally observed in these patients due to leakage of the enzymes from degenerating muscle fibers (McMillan 2011). Therefore, abnormal change criteria in the eteplirsen clinical development program were defined as $\geq 2 \times$ baseline for ALT and $\geq 3 \times$ baseline for AST.

Three (3) patients in the 30 mg/kg IV dose group, met the predefined abnormal criterion of $\geq 2 \times$ baseline for ALT. No patients in the untreated or the 50 mg/kg IV dose group met this criterion. In all 3 instances, the patient had no increase in bilirubin or GGT and a pre-treatment ALT value that was higher than the on treatment value designated as meeting the predefined abnormal criterion. The abnormal ALT values on-treatment were, therefore, considered consistent with fluctuations in ALT that may be seen with the underlying DMD.

Two (2) patients in the 30 mg/kg IV dose group had elevated AST levels that met the predefined abnormal change criterion of $\geq 3 \times$ baseline. In one case, the patient also had recorded pre-treatment ALT and AST values that were higher than the on-treatment values that met the abnormal criteria. In both cases, AST decreased with ongoing study drug, and both patients were asymptomatic. No changes were made to study drug administration, and the patients continued in the study.

In addition, 1 patient in the 30 mg/kg IV group met the predefined criterion of $\geq 1.5 \times$ ULN for bilirubin. This patients had elevated bilirubin levels prior to study drug administration that were higher than on study values. No action was taken with study drug, and the patient continues to be followed.

Overall, there were no adverse events suggestive of hepatic effect of eteplirsen, and the observed transaminase levels appeared consistent with the underlying disease.

9.5.8.4. Coagulopathy

In the 'all eteplirsen' group, 21 patients (18.4%) had a total of 42 TEAEs which were reviewed to evaluate whether they were potentially indicative of a coagulation disorder. None of the events were serious, and the majority were reported by the investigator as mild in intensity and unrelated to eteplirsen. There were no discontinuations or changes to study treatment due to any of these events, and at the time of data cutoff, all events had resolved. Three (3) patients (2.6%) had 5 TEAEs that were reported by the investigator as treatment related and/or as moderate or severe in intensity (Table 33). Four (4) events involved the Port a Cath device; in each case, there were no abnormal platelet, prothrombin time (PT), international normalized ratio (INR), or activated partial thromboplastin time (aPTT) values. Therefore, the sponsor considers these events to be not related to study drug, but rather to the Port-a-Cath device. For the event of

platelet anisocytosis, there were no concurrent events indicative of a bleeding disorder, and platelet counts, aPTT, PT, and INR were normal around the time of the reported event.

Table 33: Treatment-related and/or Moderate or Severe TEAEs Potentially Indicative of Coagulopathy

| Patient ID | Age (yr) | Dose (mg/kg) | Preferred Term | Treatment Related | Severity | Outcome |
|----------------|----------|--------------|-----------------------|-------------------|----------|-----------|
| 201/202-01-009 | 9 | 30 | Thrombosis in device | Possibly | Moderate | Recovered |
| 201/202-01-010 | 9 | 30 | Thrombosis in device | Possibly | Moderate | Recovered |
| | | | Thrombosis in device | Possibly | Moderate | Recovered |
| | | | Device occlusion | Possibly | Moderate | Recovered |
| 28-01-108 | 10 | 4 | Platelet anisocytosis | Possibly | Mild | Recovered |

Other unrelated events included infusion and injection site haematoma, prolonged aPTT, ecchymosis, thrombosis in device, catheter site haematoma, device occlusion, and petechiae.

Ten (10) patients had more than 1 adverse event potentially indicative of coagulopathy. Most of the events for the 10 patients with multiple AEs in this category were consistent with catheter site hematomas or device thrombosis. Two (2) of the 10 patients experienced events of prolonged aPTT and ecchymosis. One (1) of the 2 patients, had an elevated aPTT measurement from a normal baseline test (baseline 25.7 seconds) ranging from 36.0-53.3 seconds (normal range 23.6-32.5 seconds) on Study Days 52-95, and concurrent ecchymosis on Study Days 67-97. This patient had another asymptomatic episode of aPTT elevation (35.2 seconds) on Study Day 162-177 without an associated AE. The second patient experienced bilateral lower limb ecchymosis of 3-day duration (Study Days 501-504) 11 months prior to the onset of aPTT elevation ranging from 43.0-48.0 seconds (baseline 30.0 seconds) on Study Days 918-936. All of the events of aPTT and ecchymosis experienced by the two patients above were of mild severity and resolved without treatment.

Overall review of the events potentially related to coagulopathy suggested no consistent pattern of eteplirsen drug effect.

9.5.8.5. Infusion Site Reactions

Patients receiving eteplirsen were monitored closely for events related to potential infusion site reactions. In the analysis of infusion site reactions focus was on the eteplirsen IV group, as the route of administration for eteplirsen is IV. The 7 patients who received a single low dose of intramuscular eteplirsen in Study 33 are not included in this analysis.

In the ‘eteplirsen IV’ group, 24 patients (22.4%) had a total of 55 TEAEs which were reviewed to evaluate whether they were potentially representative of infusion site reactions. None of the events were serious, and the majority were assessed by the investigator as mild in intensity and unrelated to eteplirsen. At the time of data cutoff, the majority of events had resolved without changes to treatment administration. Two (2) patients (1.9%) each had 1 TEAE that was reported by the investigator as treatment-related and/or as moderate or severe in intensity (Table 34). The event that was considered to be possibly related resolved the same day and the patient had no

other reported infusion site reactions; and the event of moderate intensity was described as pain post-operative to port placement.

Table 34: Treatment-related and/or Moderate or Severe TEAEs Potentially Indicative of an Infusion Site Reaction

| Patient ID | Age (yr) | Dose (mg/kg) | Preferred Term | Treatment Related | Severity | Outcome |
|----------------|----------|--------------|--------------------|-------------------|----------|-----------|
| 204-233-102 | 8 | 30 | Catheter site pain | Possibly | Mild | Recovered |
| 201/202-01-010 | 9 | 30 | Catheter site pain | No | Moderate | Recovered |

Additional mild and unrelated events included catheter or infusion site haematoma (21 events in 9 patients); catheter, infusion or injection site pain (15 events in 11 patients); pyrexia (5 events in 4 patients); infusion site extravasation (4 events in 4 patients); application or infusion site erythema or rash (4 events in 3 patients); catheter site hemorrhage, inflammation, and related reaction (1 event each in 1 patient each); and infusion site swelling (1 event in 1 patient). Four (4) patients (3.7%) had their infusion interrupted as the result of a mild, unrelated TEAE of either extravasation (N = 3) or infusion site pain (N = 1).

Overall, the majority of events were mild (98.2%) and considered unrelated to eteplirsen (98.2%) and were generally reflective of the types of events due to catheter placement rather than due to a direct effect of eteplirsen.

9.5.8.6. Hypersensitivity

In the ‘all eteplirsen’ group, 27 patients (23.7%) had a total of 43 TEAEs which were reviewed to evaluate whether they were potentially representative of hypersensitivity, and 1 untreated patient (6.7%) had 1 event (mild rash). All of the events were reported as non-serious and recovered/resolved, and the majority of events in the ‘all eteplirsen’ group were mild (41/43, 95.3%) and considered by the investigator to be unrelated to study treatment (38/43, 88.4%). Study drug administration was interrupted for 2 events.

Six (6) patients (5.3%) had 7 TEAEs that were reported by the investigator as treatment related and/or as moderate or severe in intensity (Table 35). All of the events that were considered by the investigator as treatment related were mild in intensity and resolved with ongoing eteplirsen treatment; and the investigator provided an alternate etiology (‘possible reaction to Ametop plastic’) for 1 event (drug eruption) despite having recorded it as possibly related to treatment.

Table 35: Treatment-related and/or Moderate or Severe TEAEs Potentially Indicative of Hypersensitivity

| Patient ID | Age (yr) | Dose (mg/kg) | Preferred Term | Treatment Related | Severity | Outcome |
|----------------|----------|--------------|--------------------|-------------------|----------|-----------|
| 201/202-01-004 | 9 | 50 | Erythema | Possibly | Mild | Recovered |
| | | | Erythema | Possibly | Mild | Recovered |
| 201/202-01-005 | 8 | 50 | Alopecia | No | Moderate | Recovered |
| 301-218-001 | 10 | 30 | Flushing | Definitely | Mild | Recovered |
| 301-239-001 | 13 | 30 | Flushing | Possibly | Mild | Recovered |
| 201/202-01-002 | 9 | 30 | Dermatitis contact | No | Moderate | Recovered |
| 28-02-207 | 9 | 20 | Drug eruption | Possibly | Mild | Recovered |

Both events of flushing occurred on Day 1 (first infusion), resolved the same day, and did not recur despite continued dosing with eteplirsen. One (1) patient experienced 2 events of erythema (Days 974 and 988) that each occurred within 1 hour of drug infusion, resolved the same day, and did not recur despite continued dosing with eteplirsen.

There were also mild and unrelated events of rash, rash papular, rash pruritic, pruritus, erythema, urticaria, urticaria thermal, flushing, feeling hot, dermatitis contact, papule, seasonal allergy, hypersensitivity (‘worsening of seasonal allergies’), lip swelling, and swelling.

Overall, no trends or patterns in these events were observed. The time to onset from last dose ranged from 44 minutes to 7 days; the number of doses prior to event onset ranged from 1 to 199; and event duration ranged from 15 minutes (dermatitis contact) to 50 days (feeling hot). Given the resolution and lack of recurrence for most events despite continued treatment, these events appear to be reflective of the background population rather than due to study drug treatment. The 2 events, mild erythema and flushing, that occurred on the day of study drug infusion may represent potential adverse drug reactions with eteplirsen.

9.5.8.7. Infusion-related Reactions

The 7 patients who received a single low dose of intramuscular eteplirsen in Study 33 were excluded from this analysis, because IV infusion is the proposed route of administration.

In the ‘eteplirsen IV’ group, 30 patients (28.0%) had a total of 55 TEAEs which were reviewed to evaluate whether they were potentially representative of an infusion-related reaction, and 3 events occurred in 2 patients while receiving placebo. The majority of events in the ‘eteplirsen IV’ group were non-serious (54/55, 98.2%), mild in intensity (51/55, 92.7%), and unrelated to study treatment (49/55, 89.1%). None of the events required a change in treatment administration, and as of the data cutoff date, 54 of the 55 events had resolved.

Nausea and/or Vomiting

Although nausea and vomiting are relatively non-specific events and may occur in a pediatric population, these events were medically reviewed to assess whether they potentially represented a type of infusion related reaction. The overall frequency of nausea and vomiting were comparable across dose groups and not suggestive of a dose effect, ranging from 4.9 to 50.0% in

the active groups and 0 to 25.0% in the placebo group. Seven (7) patients in the ‘eteplirsen IV’ group experienced events that were moderate in intensity and/or related (possibly or definitely) to eteplirsen according to the investigator. The time to onset for these 7 events was variable with only 1 patient experiencing intermittent nausea on a day of study drug infusion. All 7 patients continued to receive study drug, and nausea or vomiting did not recur except in 2 patients. Overall, events of nausea and vomiting were not considered to represent infusion related reactions.

Pyrexia

A total 5 events of pyrexia occurred in 4 patients in the ‘eteplirsen IV’ group and 2 events occurred in 2 patients in the placebo group. All of the events were assessed by the investigator as mild in intensity and unrelated to study drug. The time to onset from last dose for the events of pyrexia ranged from 10 hours to 5 days; the number of doses prior to event onset ranged from 4 to 194; and event duration ranged from 30 minutes to 6 days with 4 of the 5 events resolving within 1 day of onset. Only 1 patient, a 9-year-old boy, experienced a recurrence of pyrexia (after dose 13 and dose 124). No trends or patterns were observed. Given the resolution and lack of recurrence for most patients despite continued treatment, and the observation of pyrexia in 2 placebo patients, it may be concluded that these events are reflective of the background population.

However, there was one case of “mild temperature elevation” coincident with study drug infusion which the investigator considered related to study drug, and this event is therefore considered a potential adverse drug reaction. ” (Patient 28-01-110 [10 mg/kg IV]) was described as a mild temperature elevation to 37.9°C after infusion of eteplirsen; this event resolved the same day, and the investigator did consider this event to be possibly related to study drug and this event is considered a potential adverse drug reaction.

Pruritus

Two (2) events of pruritus occurred in 2 patients in the ‘eteplirsen IV’ group. Both events were assessed by the investigator as mild in intensity and unrelated to study drug, and no changes were made to study treatment administration. Patient 204-201-103 (30 mg/kg IV) had a reported TEAE of pruritus from Day 106 to Day 112, and Patient 201/202-01-003 (50 mg/kg IV) had a reported TEAE of pruritus on Day 275 that resolved the same day.

Overall, non-specific symptoms of potential infusion-related reactions such as nausea and vomiting occurred in the eteplirsen-treated population at a relatively low rate, and also occurred prior to treatment or in the placebo group. Although some events have been noted on days of infusion, there was no consistent pattern of recurrence with subsequent infusions. These events were typically mild in intensity and similar across treatment groups. On review of events of pyrexia, there were no trends or patterns observed to suggest an association with study drug, as this event was also seen in the placebo group and all of the events resolved despite continued treatment. There was one case of “mild temperature elevation” coincident with infusion of eteplirsen, which the investigator considered related to study drug. This event is, therefore, considered a potential adverse drug reaction.

9.5.8.8. Severe Cutaneous Reactions

In the ‘all eteplirsen’ group, 2 patients (1.8%) had a total of 2 TEAEs (one event of mild skin erosion resulting from an accident and one event of mild dermatitis bullous that resolved without intervention within 7 days). Neither event was serious; both resolved with no change to study treatment, both were reported by the investigator as mild in intensity and unrelated to study drug.

These events were mild and self-limited without sequelae. Both had alternative etiologies, including traumatic injury and post-biopsy complication. The events were not consistent with severe cutaneous reaction.

9.5.8.9. Leukopenia/Neutropenia

In the ‘all eteplirsen’ group, 1 patient (0.9%) had 3 TEAEs that were potentially representative of leukopenia and/or neutropenia. The patient had 2 events of lymphocyte count decreased, both of which were considered by the investigator to be unrelated to treatment and mild in intensity, and 1 event of white blood cell count decreased that was mild and possibly related to treatment. All 3 events resolved with no action taken.

Given the clinical characteristics and spontaneous resolution of these events with ongoing eteplirsen treatment, there is no indication of leukocyte or neutrophil toxicity associated with eteplirsen.

9.6. Clinical Laboratory Evaluations

Laboratory parameters including hepatic tests (i.e., ALT, AST, bilirubin, alkaline phosphatase, GGT), renal function tests (i.e., BUN, creatinine), along with hematologic parameters (i.e., hemoglobin, platelet counts, leukocytes, and leukocyte differential count) and parameters related to coagulation (aPTT and PT) were reviewed. These results were discussed above in relationship to AESIs.

Overall, review of serum chemistry data did not identify safety concerns or any consistent patterns of effect that were indicative of hepatic or renal toxicity. Likewise, review of coagulation and hematologic parameters did not identify any consistent effects suggestive of a coagulation disorder or hematologic toxicity. Markedly elevated transaminase levels that decrease over time were observed and are consistent with results expected in patients with DMD.

In addition, other chemistry laboratory parameters (glucose, albumin, potassium, and creatine phosphokinase) and immunogenicity assessments were also reviewed. Increases in glucose and decreases in potassium values were observed; however, these are considered reflective of the use of corticosteroids in the study population.

Creatine kinase (CK) and immunogenicity results are presented below.

9.6.1. Creatine Kinase

Patients with DMD have grossly elevated CK values due to leakage of the enzyme from degenerating muscle fibers (Zatz 1991). Early in the disease, CK levels are usually 50 to 300 × ULN (normal range 37 to 430 U/L) as muscles degenerate, and over time, the levels tend to decrease as muscle is lost.

Overall, CK values were elevated at baseline and last observation. A total of 20 patients who received eteplirsen at 30 mg/kg or higher met the predefined criterion of $\geq 2 \times$ baseline for an abnormal change in CK value. However, in 10 of the 20 patients (30 mg/kg or higher), there was a recorded pre-treatment CK value that was higher than the reported on-treatment abnormality, and among the 20 patients, medical review determined that only 1 patient (301-210-004) had concurrent mild muscle related event (back pain lasting 5 hours), with no other reported myalgia or musculoskeletal pain. In addition, 1 untreated patient and 2 patients receiving placebo also had an increase in CK that was $\geq 2 \times$ baseline. Therefore, these abnormal CK values are considered representative of fluctuations in CK laboratory values that occur during the clinical course of DMD.

9.6.2. Immunogenicity

The potential for eteplirsen to cause immunotoxicity by complement activation was assessed in repeat-dose studies in juvenile rats, which included assays for T-cell dependent antibody response and blood immunophenotyping, and in non-human primates in complement activation assays. No biologically meaningful effects of eteplirsen on the immune system were detected in these studies.

Consistent with these findings, mean CD3, CD4 and CD8 lymphocyte counts (detected by IHC) decreased or remained stable from baseline to Week 48 in eteplirsen-treated patients in Studies 201/202, indicating a lack of immunogenicity of the newly formed dystrophin. Furthermore, there were no meaningful differences among the treatment groups in the number of interferon-gamma-induced spot-forming colonies on enzyme-linked immunosorbent spot assay (ELISPOT) from baseline through Week 48, indicating the newly expressed dystrophin in eteplirsen-treated patients did not elicit a T-cell response.

Similarly, in supportive Study 28, none of the patients had detectable levels of anti-dystrophin antibody following treatment and most of the patients in the 10 mg/kg and 20 mg/kg dose groups showed decreases in CD3, CD4 and CD8 counts. Finally, there were no clinically significant changes in immunoglobulins (IgA, IgG, or IgM) or in CD4 or CD8 counts following a single IM injection of eteplirsen in Study 33.

9.7. Therapeutic Class Effects

Even though eteplirsen being a PMO is an RNA analog, it has significant, distinct chemical and biological properties that are not seen in other RNA analogues such as phosphorothioates. The difference in the nonclinical toxicity profile between phosphorothioate-based oligonucleotides, which are negatively charged, and eteplirsen is thought to be attributed to the uncharged nature of eteplirsen's phosphordiamidate linkages that minimize protein binding and thus off-target effects.

Other RNA analogs, specifically those with phosphorothioate linkages, which are negatively charged, have been associated with renal toxicity, including increases in proteinuria (McGowan 2012; Goemans 2011). Elevated levels of transaminases, as well as an SAE of hepatic steatosis, have been observed in the context of treatment with a 2'-O-methoxyethyl (2'OME) phosphorothioate antisense oligonucleotide, mipomersen (McGowan 2012). SAEs of thrombocytopenia, as well as TEAEs related to coagulation, were observed in clinical trials of another phosphorothioate antisense oligonucleotide, drisapersen (Goemans 2014). Injection site

reactions comprised the most common TEAEs observed in clinical trials with both of these oligonucleotides, which share the common structural element of negatively-charged phosphorothioate linkages (Voit 2014, McGowan 2012).

These toxicities are dose limiting for phosphorothioate-based oligonucleotides in the clinical setting and are consistent with the nonclinical toxicity profile of phosphorothioate-based oligonucleotides (Levin 1998; Monteith 1999; Levin 2001; Henry 2008; Frazier 2014).

The safety data for eteplirsen in the clinical setting, including in 88 patients for an overall exposure of 72 patient years at the clinical dose of 30 mg/kg or higher for up to 4 years, did not suggest a signal for the above-mentioned toxicities. These clinical data for eteplirsen are consistent with the nonclinical toxicity data, which showed only non-adverse renal findings at the highest doses administered to mice and NHPs and adverse renal findings, but no other toxicities, at the highest dose level in juvenile rats (Section 4.2.2).

Unlike phosphorothioates, PMOs thus may be less likely to be associated with off-target and serum protein binding, and immune activation. Eteplirsen thus has a chemical and biological profile that is distinct from phosphorothioates.

9.8. Safety in Special Populations

9.8.1. Intrinsic Factors

The safety profile of eteplirsen was evaluated in subgroups of patients in terms of specific age groupings, BMI, race, duration since DMD diagnosis, and ambulatory status. Due to the overall small number of patients (N = 107 in the 'eteplirsen IV' group) in safety dataset, interpretation of findings is limited when the dataset is split across subgroups; in addition, interpretation is further confounded by the low number of serious, severe, and 'uncommon' TEAEs (i.e., those occurring in <10% of patients).

The overall incidence for TEAEs was 82.2% for the 'eteplirsen IV' group and was comparable across patient subgroups of age, BMI, duration since DMD diagnosis and ambulatory status. The majority of patients were between ≥ 6 and <12 years of age, and all of the very few severe or serious adverse events occurred in ambulatory children aged ≥ 6 to <12 years.

Common adverse events observed in at least 10% of patients were also evaluated by patient subgroups. The frequency of these events was generally comparable across subgroups for age, ambulatory status, and duration since diagnosis except for lower frequency rates observed in the older age groups and children with non-ambulatory status.

9.8.2. Pregnancy, Lactation, Geriatric Use

DMD is an X-linked genetic disease occurring in boys. Female carriers are, apart from extremely rare exceptions, asymptomatic. Therefore, eteplirsen has not been studied in pregnant and/or lactating women. In nonclinical testing, no evidence of eteplirsen-associated mutations, chromosomal aberrations, or clastogenic potential was observed in the ICH standard battery of genotoxicity tests. Geriatric patients have not been studied, because DMD is universally fatal during early adulthood.

10. SUMMARY OF RESULTS

10.1. Summary of Efficacy Results

Eteplirsen's ability to reliably induce the production of functional dystrophin in patients with DMD significantly slows the progression of this devastating disease as demonstrated by the following findings in eteplirsen-treated patients:

Biological Endpoints

- Confirmation of exon 51 skipping in all eteplirsen-treated patients with post-treatment biopsies (N = 36)
- *De novo* dystrophin production was demonstrated by Week 24 in Study 201 based on significant increases in the percent dystrophin positive fibers and intensity; these results were confirmed by independent, blinded pathologists
- Sustained dystrophin production was demonstrated by comparison of Study 201/202 Week 180 biopsy results to untreated controls. Utilizing methods agreed upon by FDA, significant increases in 3 complementary parameters (percent dystrophin positive fibers, dystrophin intensity, and Western Blot) were demonstrated.
- Correct localization of dystrophin at the sarcolemma, as well as localization of nNOS, and components of the DAPC at the sarcolemma, supporting the functionality of the newly expressed dystrophin protein

Primary Clinical Endpoint of 6MWT

- A significant reduction in the rate of decline for eteplirsen treated boys (N = 12) of 148 meters at Year 3 and 162 meters at Year 4 when compared to the external control group of exon 51 skippable (N = 13). Reduction in the rate of decline in 6MWT reflects amelioration of disease in terms of ambulation, endurance, and muscle function
 - Large magnitude of effect is clinically relevant (treatment effect of 148 meters (p=0.005) and 162 meters (p=0.0005) at Year 3 and Year 4 respectively)
 - Substantive reduction in the rate of decline (79 meters) even when compared to the larger, but less well matched group of any exon skipping (N = 50)
- Temporal pattern for 6MWT in both analyses is divergence of trajectories after Year 1
 - Consistent with significant dystrophin production shown at Week 24
 - Sufficient time is required for decline of comparator in order to demonstrate eteplirsen stabilization of 6MWT

Loss of Ambulation

- A significant reduction in the loss of ambulation 17% vs 85% (p=0.011) at Year 4 for eteplirsen treated boys (N = 12) vs external control (N=13), respectively.
- A substantive reduction in the loss of ambulation for eteplirsen treated boys (N = 12) with an estimated rate of 17% at Year 3 compared to an estimated rate of 46% for the external control group amenable to any exon skipping (N = 50).

Supportive Endpoints Consistently Favor Eteplirsen vs External Controls

Analyses of supportive endpoints including the percent change from baseline in NSAA total and preservation of the ability to rise from supine without external support are directionally consistent with the results of the primary outcomes of 6MWT and loss of ambulation.

- **NSAA Score:** A smaller decline in NSAA total scores over 3 years for eteplirsen boys (N = 12) compared to untreated external controls (N = 10) of 2.4 points representing loss or impairment of 2 fewer abilities.
- **Ability to Rise from Supine without External Support:** More eteplirsen treated boys were able to rise from supine without external support (55%) compared to the external control boys (8%) over 3 years.
- **Pulmonary Function Tests:** Eteplirsen treated boys had slower deterioration of respiratory muscle function as measured by FVC %predicted (decrease of ~2.5% per year) when compared to data from the published literature (5% annual decline). Additionally, MEP %predicted and MIP %predicted may also decline more slowly with eteplirsen treatment than expected, although the scientific literature on these parameters is more limited.

In summary, eteplirsen has been shown to slow the progression of DMD as measured by the 6MWT and LOA in DMD patients amenable to dystrophin exon 51 skipping over 4 years. This is supported by additional clinical measures, which are directionally consistent, including NSAA, ability to rise, and pulmonary function. The consistency of results across these endpoints supports the conclusion that eteplirsen is an effective treatment for DMD patients with genetic mutations amenable to exon 51 skipping therapy.

10.2. Summary of Safety Results

Exposure and Demography

The overall safety analysis dataset includes a total of 114 eteplirsen-treated patients; 107 patients received once weekly IV infusions of eteplirsen at doses ranging from 0.5 to 50 mg/kg and 7 received a single IM dose of 0.09 mg or 0.9 mg eteplirsen. 88 patients received eteplirsen at either the proposed dose (30 mg/kg, N = 82) or higher (50 mg/kg, N = 6), including 61 patients who received the proposed dose or higher for at least 3 months. Collectively, these data represent over 72 patient-years of safety experience at the proposed once weekly dose of 30 mg/kg or higher. A safety database of this size is not unprecedented in the rare disease setting and the accelerated approval pathway which is reserved for serious and rare diseases with a high unmet medical need.

Treatment-emergent Adverse Events

The most common ($\geq 10\%$ of patients) TEAEs occurring more frequently in patients treated with eteplirsen at either 30 or 50 mg/kg IV than in patients who received placebo were: headache, arthralgia, vomiting, upper respiratory tract infection, nasopharyngitis, cough, nasal congestion, contusion, excoriation and procedural pain. The majority of these common TEAEs were mild in severity, considered unrelated to study drug, and resolved during continued treatment with study drug.

No deaths or life-threatening events occurred during the eteplirsen clinical studies, and only 2 patients (1.8%) experienced a treatment-emergent SAE, both of which were unrelated to eteplirsen. Five (5) patients (4.4%) on eteplirsen and 1 patient in the untreated group experienced severe TEAEs, and 1 patient (0.9%) discontinued treatment prematurely due to a TEAE.

Adverse Events of Special Interest

TEAEs of special interest for the eteplirsen clinical program included medical topics that were selected based on: potential safety-related findings observed in nonclinical toxicity studies of eteplirsen (renal function), AEs associated with other RNA analogs (renal and hepatic function, coagulopathy and infusion site reactions), and general precautions with administration of a compound in clinical development (infusion-related reactions, hypersensitivity, severe cutaneous reactions, leukopenia and neutropenia). Inclusion of adverse events associated with other RNA analogs in Adverse Events of Special Interest for eteplirsen, is a conservative approach, since eteplirsen is structurally dissimilar and the nonclinical toxicity data for eteplirsen did not show a signal except for renal findings at high doses.

Renal function

Twenty-one (21) TEAEs potentially representative of renal toxicity were reported in 16 patients (14.0%) in the ‘all eteplirsen’ group, and an event of proteinuria was reported in both a placebo patient and a 30 mg/kg patient prior to treatment initiation. All of the events were mild; the majority were transient and spontaneously resolved with ongoing study drug administration. Proteinuria/urine protein present were the most common events observed; these events were transient or sporadic, spontaneously resolved with ongoing treatment, and were not associated with increasing renal laboratory values, with the exception of 1 patient who had adverse events of increased BUN and increased creatinine in the setting of dehydration.

Review of renal adverse events and laboratory parameters identified no pattern of drug effect.

Cardiac function:

Twelve (12) TEAEs potentially indicative of a cardiac disorder were reported in 6 patients in the ‘all eteplirsen’ group. These events included tachycardia and cardiomyopathy which are known to occur in the background population. None of the events were serious, and the majority were assessed by the investigator as mild in intensity and as possibly related to eteplirsen with the exception of a severe case of cardiomyopathy, which resulted in study drug discontinuation.

Echocardiogram data in the ongoing Study 201/202 did not suggest any pattern of decline in left ventricular ejection fraction for the 12 patients on eteplirsen at 30 or 50 mg/kg/wk for 4 years.

Based on the known prevalence (27%) of cardiomyopathy in patients with DMD, it is difficult to establish a causal association with drug therapy.

Hepatic function:

There have been no reported adverse events suggestive of drug-induced hepatotoxicity.

Coagulopathy: Forty-two (42) TEAEs potentially indicative of a coagulation disorder were reported in 21 patients (18.4%) in the ‘all eteplirsen’ group. None of the events were serious, and the majority were reported by the investigator as mild in intensity and not related to eteplirsen. Overall review of the events potentially related to coagulopathy suggested no consistent pattern of eteplirsen drug effect.

Infusion site reactions: Fifty-five (55) infusion site reactions were reported in 24 patients (22.4%) in the ‘eteplirsen IV’ group with over 3900 infusion (event rate <1.5%). Events of catheter-related pain, hematoma, or infusion site extravasation occurred during clinical studies of eteplirsen, but were generally reflective of the types of events due to catheter placement rather than due to a direct effect of eteplirsen. These events were all transient, mostly mild in severity, and consistent with catheter-related complications, which does not suggest an association with eteplirsen.

Infusion related reactions: Fifty-five (55) TEAEs were reported in 30 patients (28.0%) in the ‘all eteplirsen IV’ dose group and 3 events were reported in 2 placebo patients (50.0%). Non-specific symptoms of potential infusion-related reactions such as nausea and vomiting occurred in the eteplirsen-treated population at a relatively low rate, and also occurred prior to treatment or in the placebo group. Although some events have been noted on days of infusion, there was no consistent pattern of recurrence with subsequent infusions. There was one case of “mild temperature elevation” (coded to the Preferred Term “Infusion related reaction”) coincident with infusion of eteplirsen, which the investigator considered possibly related to study drug. This event is, therefore, being considered a potential adverse drug reaction.

Hypersensitivity: A total of 43 TEAEs potentially representative of hypersensitivity were reported in 27 patients (23.7%) in the ‘all eteplirsen’ group. None of the events were serious, and the majority were reported by the investigator as mild in intensity and not related to eteplirsen. There have been reports of mild and unrelated rash, contact dermatitis, papule, urticaria and pruritus coincident with eteplirsen treatment. There were no trends or patterns in time to onset from last dose, the number of doses prior to event, or event. Given the resolution and lack of recurrence for most events with continued treatment it may be concluded that these events are reflective of the background population rather than due to study drug treatment. There have been mild events of erythema and flushing occurring on days of study drug infusion, which may represent potential adverse drug reactions with eteplirsen.

Severe cutaneous reactions: Two (2) TEAEs potentially indicative of a severe cutaneous reaction were reported in 2 patients (1.8%) in the ‘all eteplirsen’ group. These events were mild and self-limited without sequelae. Both had alternative etiologies, including traumatic injury and post-biopsy complication. The events were not consistent with severe cutaneous reaction.

Leukopenia and neutropenia

The potential for leukopenia/ neutropenia was evaluated by review of TEAE data as well as pertinent laboratory parameters. TEAEs of mild leukopenia and lymphopenia were reported for a single patient. Both the leukocyte and lymphocyte counts subsequently normalized with ongoing eteplirsen treatment. There were no reported TAEs of neutropenia. Across all patients, evaluation of leukocytes, neutrophils, and lymphocytes identified no consistent pattern suggestive of drug effect.

Safety will continuously be evaluated in the post-marketed setting including spontaneous adverse event reports, reports from ongoing clinical studies and other sources. In addition a planned longitudinal observational safety registry in DMD patients will collect safety assessments including adverse events of special interest.

In summary, eteplirsen has been shown to be well tolerated, with low rates of serious or severe adverse effects, and the most common events are likely characteristic of the background

population. The following common events occurred more frequently in patients who received 30 or 50 mg/kg eteplirsen IV than in patients who received placebo: headache, vomiting, cough, procedural pain, upper respiratory tract infection, arthralgia, contusion, excoriation, nasopharyngitis and nasal congestion. Due to their temporal occurrence relative to eteplirsen administration, the following events will be categorized as ADRs: erythema, flushing, and mild temperature elevation.

11. BENEFITS AND RISKS CONCLUSIONS

11.1. Medical Need

Duchenne muscular dystrophy is a rare, degenerative neuromuscular disease caused by mutations in the *DMD* gene leading to progressive muscle degeneration and ultimately death by early adulthood (Brooke 1989; Eagle 2002; Kohler 2009).

There are no approved therapies for DMD in the US. Although glucocorticoids may be used, their modest effects on delaying disease progression are accompanied by significant side effects. (Beenakker 2005; Biggar 2006; Pradhan 2006; Manzur 2009; Schram 2013; Henricson 2013a). Therefore, there remains a high unmet medical need for an effective therapy for these patients.

11.2. Benefits of Eteplirsen

Eteplirsen is a disease-modifying PMO therapeutic for DMD patients with mutations that are amenable to skipping exon 51. Clinical trials have demonstrated that, in this specific DMD population, eteplirsen treatment induced dystrophin expression resulting in the following sustained clinical benefits:

- Eteplirsen treated patients demonstrated significantly better performance on the 6MWT versus an untreated external control cohort bearing exon 51 skippable mutations, with a clinically meaningful 148 (p=0.005) and 162 meter (p=0.0005) advantage after 3 and 4 years of therapy, respectively.
- Fewer eteplirsen-treated patients lost ambulation over the course of 4 years (2/12) compared to untreated external controls (10/13). In a Kaplan-Meier analysis an estimated 17% eteplirsen-treated patients lost ambulation, compared with an estimated 85% (p=0.011) for the external control group amenable to exon 51 skipping (N = 13).
- Treatment with eteplirsen resulted in a slower rate of decline on the NSAA total score compared to untreated external control patients over 3 years; this was consistent with results for the 6MWT.
- Eteplirsen treated patients experienced relative pulmonary function stability (yearly decline of approximately 2.5% of FVC% predicted) compared to published natural history data (annual decline of 5% of FVC% predicted).

11.3. Risks of Eteplirsen

Clinical trials have evaluated safety in a total of 114 patients with DMD, 88 of whom received a dose of ≥ 30 mg/kg. Sixty one of the 88 patients received a weekly dose of 30 mg/kg eteplirsen for at least 3 months.

- The favorable tolerability of eteplirsen is demonstrated by low rates of treatment emergent SAEs (N = 2, 1.8%), severe AEs (N = 5, 4.4%), and AEs resulting in study drug discontinuation (N = 1, 0.9%).
- The most common ($\geq 10\%$ of patients) TEAEs occurring more frequently in patients treated with eteplirsen at either 30 or 50 mg/kg IV than in patients who received

placebo were: headache, arthralgia, vomiting, upper respiratory tract infection, nasopharyngitis, cough, nasal congestion, contusion, excoriation and procedural pain.

- Due to their temporal relationship to eteplirsen administration, the following events are also categorized as ADRs: erythema, flushing, and mild temperature elevation.
- Adverse events of special interest in the following medical categories were not considered related to eteplirsen treatment (i.e. renal toxicity, hepatotoxicity, cardiac-related events, coagulopathy, severe cutaneous reactions, and leukopenia).

11.4. Benefit: Risk Conclusions

The favorable benefit: risk profile of eteplirsen is demonstrated by the totality of evidence showing that weekly administration of eteplirsen is well-tolerated, and is an effective treatment in patients with DMD who are amenable to exon 51 skipping therapy. Specifically, eteplirsen slows the rate of decline in ambulation, endurance, and muscle function as measured by the 6MWT over a 4-year treatment period compared to external control data. Sarepta is committed to the completion of confirmatory trials that will not only aim to verify the clinical benefit of eteplirsen using the 6MWT (intermediate endpoint for accelerated approval), but will also provide an evolving understanding of the safety profile.

The benefits of eteplirsen are demonstrated by a significant difference in the 6MWT of 162 meters compared to external control and a reduction in the number of boys with an estimated loss of ambulation (17% for eteplirsen compared to 85% (p=0.011) for the external control cohort of exon 51 skippable patients). Given the highly comparable nature of the eteplirsen patients to the external control including baseline age, 6MWT distance and longitudinal use of steroids, this difference can only be reasonably attributed to the beneficial intervention of eteplirsen. Moreover, additional clinical assessments using the NSAA and PFTs are supportive of the beneficial clinical effect of eteplirsen as well. In addition, to the demonstrated clinical benefit, the biologic endpoints confirm the predicted mechanism of action and that *de novo* dystrophin production occurs when boys are treated with eteplirsen.

Significantly, this clinical benefit is accompanied by a safety profile that indicates that eteplirsen is well tolerated with no apparent signal of safety risks. Although the safety dataset of 114 patients may not detect rare events and therefore carries the potential risk of uncertainty in characterization of such events, this needs to be weighed against the certainty of relentless disease progression and premature death for boys with DMD without treatment.

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APPENDIX 1. KEY FDA REGULATORY INTERACTIONS REGARDING ETEPLIRSEN

| Date | Summary of Key Regulatory Activity |
|-------------|--|
| 02 Aug 2007 | AVI BioPharma (AVI) submits an initial IND for eteplirsen. |
| 23 Oct2007 | FDA grants orphan drug designation to eteplirsen for the treatment of DMD |
| 27 Nov 2007 | FDA designates the investigation of eteplirsen for the treatment of DMD as Fast Track development program |
| 25 Apr 2011 | <p>AVI submits a new proposed clinical protocol for study 4658-us-201, a randomized, double-blind, placebo-controlled, 24-week study of eteplirsen with two arms:</p> <ul style="list-style-type: none"> • 50 mg/kg eteplirsen IV and matched placebo with a 12-week on-treatment biopsy time point • 30 mg/kg eteplirsen IV and matched placebo with a 24-week on-treatment biopsy time point |
| 14 Jun 2011 | <p>A Type B End-of-Phase 1 meeting is held between the FDA and AVI. Key issues discussed at this meeting are:</p> <ul style="list-style-type: none"> • Surrogate endpoints: FDA states that a statistically significant finding on a clinically meaningful functional outcome would be needed to support an efficacy claim for eteplirsen, and that findings on biomarkers and exploratory functional endpoints could only be supportive • Extension study: FDA agrees that an open-label rollover study, 4658-us-202, may initiate at the end of study 201 • Juvenile toxicology study: FDA makes various recommendations for the design of a 10-week repeat-dose toxicology study of eteplirsen in juvenile rats, including an assessment of immune function • FDA agrees that analysis of complement activation in the 9-month repeat dose cynomolgus monkey study will suffice to assess complement activation in NHPs |
| 12 Jul 2012 | AVI BioPharma changes its name to Sarepta Therapeutics |

| Date | Summary of Key Regulatory Activity |
|-------------|---|
| 13 Mar 2013 | <p>A Type B End-of-Phase 2 (EOP2) meeting held between FDA and Sarepta. Key issues discussed at this meeting are:</p> <ul style="list-style-type: none"> • Accelerated approval: FDA considers the study 201/202 dataset through Week 48 of the combined studies to be inadequate to support accelerated approval for the following reasons: <ul style="list-style-type: none"> ○ No difference observed in the 6MWT in study 201 based on the ITT analysis ○ 6MWT results in study 202 are uninterpretable due to the uncontrolled, open-label study design, and the effort-dependent nature of the 6MWT ○ Inadequate characterization of the quantity of dystrophin in treated patients, due to the lack of western blot data ○ Dystrophin as assessed by IHC appears of lesser quantity than in BMD ○ “No good correlation” observed between the dystrophin and 6MWT results in 201/202 <p>FDA concludes that Sarepta should submit further information to support the use of dystrophin as a surrogate endpoint, as well as a discussion of all clinical functional outcomes assessed in eteplirsen studies , in order to determine whether it will consider filing an NDA for accelerated approval</p> <ul style="list-style-type: none"> • Confirmatory study design: Sarepta proposes study 4658-301 (named PROMOVI), an open-label study of eteplirsen in exon 51 skipping amenable DMD patients, versus a concurrent untreated cohort of DMD patients with exon deletions not amenable to skipping exon 51, as a confirmatory study to support accelerated approval of eteplirsen. FDA indicates that placebo control is seemingly necessary to provide interpretable data of an effect on the 6MWT beyond the known variability range of DMD. • Safety population: FDA requires that additional exposed patients beyond the existing 38 in order to conclude that the drug has an acceptable risk/benefit profile. |
| 23 Jul 2013 | <p>A Type C guidance meeting is held between the FDA and Sarepta as a follow-up to the March 2013 EOP2 meeting.</p> <ul style="list-style-type: none"> • FDA states that based on additional information submitted on dystrophin and clinical outcomes; “We are now open to considering an NDA based on these data for filing”. <p>FDA also makes the following general recommendations:</p> <ul style="list-style-type: none"> • Creation of a proposed charter for dystrophin quantification methods to be used in future biopsies • Independent confirmation of the dystrophin-positive fiber results from study 201/202 • Collaborative development of a protocol for either a western blot or dot blot method to quantify total protein • Obtaining and analyzing a fourth biopsy from patients in study 201/202 • Obtaining additional safety data |

| Date | Summary of Key Regulatory Activity |
|-------------|---|
| 08 Nov 2013 | <p>A Type C guidance meeting is held between the FDA and Sarepta to discuss the design of PROMOVI, and determine whether it will be placebo-controlled or open label.</p> <ul style="list-style-type: none"> • In preliminary comments received November 6th, FDA states that the negative reports of the large Phase 3 drisapersen study and Phase 2 PTC124 study, two drugs also thought to act by increasing dystrophin, “raises considerable doubt about the biomarker (dystrophin), and consequently, its ability to reasonably likely predict clinical benefit”. Taken in combination with perceived difficulties in interpretation of the 6MWT results from studies 201/202, FDA “currently consider an NDA filing for eteplirsen as premature” • FDA also stated that “further biopsies should be delayed until a “validated assay to quantify dystrophin becomes available.” • Sarepta’s presentation for this meeting focuses on the chemical differences eteplirsen and drisapersen (i.e. the oligomer backbone and nucleobase sequence), the lack of publicly available evidence that drisapersen adequately induces either exon skipping or <i>de novo</i> dystrophin expression, and the superiority of eteplirsen over drisapersen reported in vivo (Heemskerk 2009). |
| 15 Nov 2013 | <p>A teleconference is held between the FDA and Sarepta to continue the discussion from the November 8th Type C meeting regarding the design of PROMOVI.</p> <ul style="list-style-type: none"> • Sarepta discusses the projected difficulty of enrolling a 120-patient placebo-controlled study of eteplirsen in the United States. • FDA concludes that it may be open to the open-label design of PROMOVI if analysis of DMD natural history data were to reveal subgroups with high degrees of predictability of decline on the 6MWT. |
| 13 Dec 2013 | <p>FDA requests the methodology and protocols used for the dystrophin-positive fiber, dystrophin intensity, western blot, and RT-PCR assays in study 201/202</p> |
| 19 Dec 2013 | <p>A Type A guidance meeting is held between the FDA and Sarepta to continue discussion on the design of PROMOVI, including presentation of the study 201/202 Week 96 6MWT data.</p> <ul style="list-style-type: none"> • FDA requests that Sarepta contact the sponsors of the Italian Telethon and Belgian DMD natural history databases and request that their raw be provided to the FDA for analysis. • FDA also recommends that Sarepta develop a plan to assess the immunogenicity of eteplirsen. • FDA concludes that it is not prepared to take a position on the open label design of the proposed confirmatory trial, nor resume a position on the feasibility of filing an NDA for eteplirsen based on the current dataset. |

| Date | Summary of Key Regulatory Activity |
|--------------------|---|
| 07 Feb 2014 | <p>An ad hoc teleconference is held between the FDA and Sarepta. The FDA requests all of the biomarker images and data listings from study 201/202 for review:</p> <ul style="list-style-type: none"> • Dystrophin-positive fibers by IHC • Fluorescent intensity of dystrophin by BIOQUANT • Total protein by western blot • Exon skipping by RT-PCR |
| 20 Feb 2014 | <p>Sarepta completes submission of all of the requested biomarker data</p> |
| 19 Mar 2014 | <p>A guidance meeting is held between the FDA and Sarepta.</p> <ul style="list-style-type: none"> • FDA states that it is open to filing an NDA for eteplirsen for consideration under accelerated approval • FDA proposed a potential approach of two confirmatory studies, an open-label study of eteplirsen and a randomized, double-blind, placebo-controlled trial of another exon skipping PMO • In order for FDA reviewers to better understand the dystrophin-positive fiber methodology, FDA reviewers will visit the laboratory where the dystrophin assessments in study 201/202 were conducted. <p>FDA adds the following remaining reservations regarding the 201/202 dataset, which it states will be NDA review issues:</p> <ul style="list-style-type: none"> • The 6MWT analysis is based on a modified ITT population, excluding the two patients who became non-ambulant during study 201 • The supportive care given to 201/202 patients versus patients in a historically-controlled population • Potential bias in administration of the 6MWT during the open-label study 202 |
| 21 Mar 2014 | <p>In accordance with verbal agreement at the March 19th meeting, Sarepta sends correspondence to FDA outlining a new proposed clinical development plan for eteplirsen, including:</p> <ul style="list-style-type: none"> • the open-label confirmatory study PROMOVI, • a safety study of eteplirsen in DMD patients with advanced disease (4658-204), • a safety study of eteplirsen in 4- to 6-year-olds (4658-203), • a randomized, placebo-controlled confirmatory study of SRP-4045 and SRP-4053 in a pooled population of DMD patients amenable to skipping exons 45 and 53 (protocol 4045-301, named ESSENCE) • Sarepta also commits to collaborating with FDA in development of bioassay methods for analysis of dystrophin in future biopsies. |

| Date | Summary of Key Regulatory Activity |
|-------------|---|
| 15 Apr 2014 | <p>FDA sends an advice letter verifying that an NDA for eteplirsen should be fileable based on the available dataset, and identifies additional data needed to support the efficacy and safety of eteplirsen. FDA proposes two potential pathways to accelerated approval:</p> <ul style="list-style-type: none"> • Considering the 6MWT data from 201/202 as a finding on an intermediate clinical endpoint • Considering quantification of dystrophin in muscle biopsies via a number of modalities as a surrogate endpoint <p>FDA identifies two confirmatory trials to verify clinical benefit and urges Sarepta to initiate both studies as soon as possible:</p> <ul style="list-style-type: none"> • A historically-controlled study of eteplirsen (PROMOVI) • A randomized, placebo-controlled study of another PMO with a similar mechanism of action, directed at a different exon (ESSENCE) <p>FDA makes the following requirements for NDA filing:</p> <ul style="list-style-type: none"> • Obtain and submit patient-level historical control data, establishing that treatment modalities were similar to the 201/202 patients • Submitting additional patient exposure data beyond the existing 38 patients <p>FDA remains “skeptical” of the existing biomarker data and provides the following recommendations:</p> <ul style="list-style-type: none"> • A collaborative effort between the FDA and Sarepta to develop a better understanding of the methods and analyses used for generation of the existing biomarker data and aid the development of suitable, consistent, and objective methods for collection and analysis of additional biomarker data • A fourth biopsy of patients in study 202, with the samples compared in a blinded fashion to samples obtained from treatment-naïve patients with exon 51 skipping amenable DMD • Extending the duration of PROMOVI open-label confirmatory trial beyond 48 weeks |
| 09 May 2014 | <p>Protocol 4658-301, entitled “<i>An Open-Label Multi-center, 48-Week Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in DMD</i>” (PROMOVI) is submitted to the IND to initiate the first confirmatory trial.</p> |
| 03 Jul 2014 | <p>Protocol 4658-204, entitled “<i>An Open-Label Multi-center Study to evaluate the Safety and Tolerability of Eteplirsen in patients with Advanced Stage DMD</i>” is submitted to the IND to initiate the study.</p> |
| 29 Jul 2014 | <p>FDA sends an advice letter requesting that Sarepta arrange for reassessment of the raw IHC images for determination of dystrophin-positive fibers from studies 201/202 and 28 by three independent experts, including assessment of the inter- and intra-operator reliability</p> |

| Date | Summary of Key Regulatory Activity |
|-------------|--|
| 18 Sep 2014 | <p>A Type B Pre-NDA meeting is held between FDA and Sarepta. FDA states that in addition to the available data, the following supplementary data are required to be included in the initial NDA submission in order to accept (file) the application for review:</p> <ul style="list-style-type: none"> • 3-month safety data from at least 12 to 24 newly exposed patients • Results of the University of Florida MRI natural history study • Patient-level historical control data on clinical endpoints, including timed tests, baseline factors, and ancillary care • Blinded reassessment of dystrophin-positive fiber data from studies 201/202 and 28 by 3 independent pathologists • Week 168 efficacy data from study 201/202 • Presentation and analysis of the historical data available regarding dystrophin expression in BMD, including correlation between protein level and phenotype |
| 15 Oct 2014 | <p>FDA and Sarepta hold an ad hoc teleconference to discuss a design for the blinded reassessment of IHC images from study 201/202</p> |
| 28 Oct 2014 | <p>FDA sends correspondence regarding on Sarepta’s proposed protocol for reassessment of IHC images from study 201/202, including comments that:</p> <ul style="list-style-type: none"> • Quantification of protein level, which is not provided by the dystrophin-positive fiber assay, will be a “key” NDA review consideration • The primary statistical endpoint of the reassessment should be the baseline samples versus Weeks 12 and 24, as the Week 48 biopsy was taken from a different muscle type (deltoid vs. biceps) and processed in a separate batch, either of which could introduce confounding factors |
| 14 Nov 2014 | <p>FDA agrees to Sarepta’s revised protocol for reassessment of IHC images from study 201/202</p> |

| Date | Summary of Key Regulatory Activity |
|-------------|--|
| 18 Nov 2014 | <p>A Type A guidance meeting is held between the FDA and Sarepta to discuss and agree on the design of the second proposed confirmatory study to support accelerated approval of eteplirsen. FDA and Sarepta agree to the following design aspects:</p> <ul style="list-style-type: none"> • Randomized, double-blind, placebo control • A pooled study of SRP-4045 and SRP-4053 at a 30 mg/kg/week dose each • A patient population aged 7 to 16 years with a baseline 6MWT distance 300 to 450 meters and receiving a stable dose of oral corticosteroids • A primary endpoint of the 6MWT • Secondary endpoints of PFTs, dystrophin-positive fibers, protein level by western blot, the NSAA, and timed function tests • A 48-week duration • A total sample size of 99 patients, allocated to placebo or treatment in a 2:1 ratio |
| 23 Jan 2015 | <p>Protocol 4658-203, entitled “<i>An Open-Label Multi-center Study to evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-Stage DMD</i>” is submitted to the IND to initiate the study.</p> |
| 30 Mar 2015 | <p>FDA agrees that analysis of the Week 180 fourth biopsy tissue samples from study 202 may proceed with the assay protocols for western blot, dystrophin-positive fibers, dystrophin intensity, and RT-PCR submitted by Sarepta</p> |
| 19 May 2015 | <p>A Type C Pre-NDA meeting is held between FDA and Sarepta, as a follow-up to the September 18th Pre-NDA meeting. FDA states that Sarepta’s proposed outline of the NDA is “generally acceptable” and requests submission of the following data to the NDA as soon as possible:</p> <ul style="list-style-type: none"> • Week 192 efficacy data from study 201/202 • Week 180 fourth biopsy data • FDA accepts that Sarepta was unable to obtain patient-level PFT natural history data from the Cooperative International Neuromuscular Research Group (CINRG), but requests that Sarepta continue efforts to obtain these data. • Sarepta states that they will submit the NDA as a rolling submission. |
| 20 May 2015 | <p>Sarepta initiates the rolling NDA submission by providing the chemistry, manufacturing and control (CMC) and nonclinical portions of the NDA</p> |
| 26 Jun 2015 | <p>Sarepta submits the clinical portion of the NDA, completing the rolling NDA submission</p> |

| Date | Summary of Key Regulatory Activity |
|-------------|--|
| 25 Aug 2015 | FDA accepts (files) the NDA for review and grants priority review designation, setting the user fee goal date of 26 February 2016 |
| 22 Oct 2015 | The NDA Mid-Cycle Communication Meeting is held between FDA and Sarepta |
| 10 Dec 2015 | FDA requests functional efficacy data (including 6MWT) from the Study 201/202 Week 216 time point |
| 14 Dec 2015 | Sarepta provides the Study 201/202 Week 216 efficacy data |
| 08 Jan 2016 | Sarepta provides Year 4 6MWT and loss of ambulation data for the exon 51 skipping amenable external control patients |
| 11 Jan 2016 | The NDA Late-Cycle Meeting is held between FDA and Sarepta |
| 20 Jan 2016 | The FDA postpones the planned January 22nd PCNS Drugs Advisory Committee meeting for eteplirsen due to a weather emergency |
| 05 Feb 2016 | FDA extends the PDUFA date for the eteplirsen NDA by 3 months to 26 May 2016. Sarepta's submission of the additional 4-year external control data on 8 January 2016 is considered to be a major amendment and the delay to the NDA action date is "to provide time for a full review of the submission." |

APPENDIX 2. INCLUSION AND EXCLUSION CRITERIA STUDY STUDY 201/202

Inclusion Criteria Study 201

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] \geq 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 \pm 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.

Exclusion Criteria Study 201

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.

Inclusion Criteria Study 202

In order to be considered eligible, all of the following criteria must have been met:

1. The patient and/or their parent/legal guardian are willing and able to provide signed informed consent.
2. The patient has successfully completed 28 weeks of treatment in Study 4658-us-201.
3. The patient has a parent(s) or legal guardian(s) who is able to understand and comply with all of the study procedure requirements.

Exclusion Criteria Study 202

Patients who met any one of the following criteria were ineligible for participation in the study:

1. The patient has a prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient or make it unlikely that the course of treatment or follow-up would be completed or impair the assessment of study results.

APPENDIX 3. BASELINE CHARACTERISTICS STUDY 201/202 ETEPLIRSEN-TREATED (N = 12)

| SOURCE | SUBJ. | Deleted Exon(s) | AGE (YRS) | HEIGHT (CM) | WEIGHT (KG) | 6MWT (M) | NSAA (TOTAL SCORE) | Baseline Rise Time (s) | Ability to Rise without External Support at Baseline (Y/N) | STEROID, DOSE, & REGIMEN (Dose: mg or mg/kg†) | | |
|--------------------------|-------|-----------------|-----------|-------------|-------------|----------|--------------------|------------------------|--|---|------|--------------|
| | | | | | | | | | | | | |
| Eteplirsen Study 201/202 | 002 | 48-50 | 9.03 | 117 | 24.8 | 416 | 28 | 3.2 | Y | DFZ | 18 | Continuous |
| | 003 | 49-50 | 7.29 | 118 | 23.7 | 366 | 31 | 4.3 | Y | DFZ | 18 | Continuous |
| | 004 | 45-50 | 8.79 | 117 | 27.4 | 389 | 27 | 3.1 | Y | DFZ | 24 | Continuous |
| | 005 | 50 | 8.01 | 117 | 23.5 | 374 | 23 | 8.2 | Y | DFZ | 21 | Continuous |
| | 006 | 52 | 10.53 | 131 | 35.1 | 355 | 17 | 12 | N* | DFZ | 21 | Continuous |
| | 007 | 49-50 | 8.02 | 120 | 40.9 | 374 | 30 | 4.6 | Y | PRD | 20 | Continuous |
| | 008 | 49-50 | 10.49 | 117 | 35 | 346 | 23 | 4.9 | Y | DFZ | 22.5 | Continuous |
| | 009 | 45-50 | 9.79 | 138 | 39.8 | 330 | 21 | 6.3 | Y | PRD | 25 | Continuous |
| | 010 | 45-50 | 9.79 | 136 | 39.7 | 256 | 17 | 12.7 | Y | PRD | 25 | Continuous |
| | 012 | 49-50 | 10.95 | 133 | 38.3 | 351 | 27 | 12 | Y | PRD | 75 | Intermittent |
| | 013 | 45-50 | 10.58 | 126 | 34.2 | 400 | 24 | 6 | Y | DFZ | 22.5 | Continuous |
| | 015 | 52 | 9.6 | 117 | 26.8 | 401 | 31 | 3.5 | Y | DFZ | 15 | Continuous |

Abbreviations: DFZ = Deflazacort; PRD = Prednisone;

Note in the table of baseline characteristics, rows for patients with loss of ambulation during 3 years of follow-up are shaded.

Ability to Rise without External support defined as score of 1 or 2 on “Rise from Floor” (NSAA item 11)

*Eteplirsen Patient 006 unable to rise w/o external support at baseline but subsequently had (and maintained) ability to Year 4

APPENDIX 4. BASELINE CHARACTERISTICS EXTERNAL CONTROL GROUP (N = 13)

| SOURCE | SUBJ. | Deleted Exon(s) | AGE (YRS) | HEIGHT (CM) | WEIGHT (KG) | 6MWT (M) | NSAA (TOTAL SCORE) | Baseline Rise Time (s) | Ability to Rise without External Support at Baseline (Y/N) | STEROID, DOSE, & REGIMEN (Dose: mg or mg/kg†) | | |
|------------------|-------|-----------------|-----------|-------------|-------------|----------|--------------------|------------------------|--|---|------|--------------|
| | | | | | | | | | | | | |
| LNMRC | ECG1 | 50 | 11.8 | 136 | 46 | 327 | UNK | N/A | N | DFZ or Equiv. | UNK | Continuous |
| | ECG2 | 52 | 11.5 | 132 | 34.6 | 451 | UNK | 4.97 | Y | DFZ or Equiv. | UNK | Continuous |
| | ECG3 | 45-50 | 8.6 | 107 | 17.0 | 355 | UNK | 3.62 | Y | DFZ or Equiv. | UNK | Continuous |
| Italian Telethon | ECM1 | 48-50 | 11.5 | 133 | 47 | 200 | 10 | N/A | N | DFZ | 0.8 | Continuous |
| | ECM2 | Ex 50 | 8.6 | 135 | 48 | 380 | 31 | 2.9 | Y | DFZ | 0.9 | Intermittent |
| | ECM3 | 52 | 9 | 130 | 28 | 373 | 24 | 4.09 | Y | PRD | 0.75 | Intermittent |
| | ECM4 | 45-50 | 8.83 | 136 | 42 | 329 | 24 | 7.1 | Y | DFZ | 0.9 | Continuous |
| | ECM5 | 49-50 | 9.3 | 131 | 44 | 295 | 15 | 6.2 | Y | DFZ | 0.9 | Intermittent |
| | ECM6 | 49-50 | 8 | 131 | 33 | 380 | 23 | 6 | Y | DFZ | 0.8 | Continuous |
| | ECM7 | 45-50 | 7.33 | 131 | 26 | 325 | 29 | 2.37 | Y | DLT | 17.5 | Continuous |
| | ECM8 | 52 | 10.2 | 126 | 27.1 | 458 | 25 | 5.66 | Y | DFZ | 0.9 | Continuous |
| | ECM9 | 48-50 | 10.1 | 133 | 31 | 388 | 20 | 10.0 | Y | PRD | 0.75 | Intermittent |
| | ECM10 | 49-50 | 8.1 | 127 | 39 | 388 | 19 | 9.0 | Y | PRD | 0.75 | Intermittent |

Abbreviations: DFZ = Deflazacort; PRD = Prednisone; DLT = Deltacortene; UNK = Unknown

Note in the table of baseline characteristics, rows for patients with loss of ambulation during 3 years of follow-up are shaded.

Ability to Rise without External support defined as score of 1 or 2 on “Rise from Floor” (NSAA item 11)

APPENDIX 5. LONGITUDINAL 6MWT AND NSAA, ETEPLIRSEN TREATED (N=12)

| Source | Subject | Year 6MWT (m) | | | | | NSAA Total Score | | | | |
|-----------------------------|---------|------------------|-----|-----|-----|-----|------------------|----|----|----|----|
| | | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| Eteplirsen Study 201/202 | 2 | 416 | 430 | 416 | 378 | 349 | 28 | 26 | 27 | 25 | 14 |
| | 3 | 366 | 444 | 425 | 324 | 192 | 31 | 24 | 18 | 7 | 4 |
| | 4 | 389 | 371 | 331 | 355 | 221 | 27 | 23 | 21 | 24 | 10 |
| | 5 | 374 | 302 | 293 | 247 | 143 | 23 | 22 | 14 | 8 | 4 |
| | 6 | 355 | 326 | 346 | 359 | 332 | 17 | 16 | 19 | 13 | 14 |
| | 7 | 374 | 304 | 354 | 312 | 197 | 30 | 20 | 20 | 13 | 11 |
| | 8 | 346 | 303 | 255 | 100 | 55 | 23 | 21 | 17 | 13 | 6 |
| | 9 | 330 | 0 | 0 | 0 | 0 | 21 | 5 | 2 | NP | 0 |
| | 10 | 256 | 0 | 0 | 0 | 0 | 17 | 4 | 1 | 1 | 0 |
| | 12 | 351 | 330 | 314 | 298 | 237 | 27 | 20 | 18 | 11 | 8 |
| | 13 | 400 | 368 | 367 | 301 | 230 | 24 | 20 | 21 | 14 | 8 |
| | 15 | 401 | 492 | 450 | 483 | 400 | 31 | 32 | 30 | 25 | 18 |

NP: Not performed

APPENDIX 6. LONGITUDINAL 6MWT AND NSAA, EXTERNAL CONTROL GROUP

| Source | Subject | Year 6MWT (m) | | | | | NSAA Total Score | | | |
|---------------------|---------|------------------|--------|-------|-------|--------------------|------------------|------|------|------|
| | | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 |
| Italian Telethon | ECM1 | 200.0 | 210.0 | 0.0 | 0.0 | 0.0 | 10.0 | 8.0 | 4.0 | NP |
| | ECM2 | 380.0 | 352.0 | 326.0 | 195.0 | ND [‡] | 31.0 | 26.0 | 20.0 | 14.0 |
| | ECM3 | 373.3 | 259.0 | 305.0 | 273.0 | 0.0 | 24.0 | 13.0 | 11.0 | 8.0 |
| | ECM4 | 329.0 | 298.44 | 230.0 | 218.0 | 0.0 | 24.0 | 22.0 | 13.0 | 12.0 |
| | ECM5 | 295.0 | 307.0 | 153.0 | 35.0 | 0.0 | 15.0 | 13.0 | 12.0 | 9.0 |
| | ECM6 | 380.0 | 285.0 | 250.0 | 0.0 | 0.0 | 23.0 | 13.0 | 7.0 | 3.0 |
| | ECM7 | 325.0 | 301.8 | 210.0 | 0.0 | 0.0 | 29.0 | 27.0 | 13.0 | 3.0 |
| | ECM8 | 458.0 | 495.0 | 435.0 | 362.0 | 300.0 [†] | 25.0 | 26.0 | 25.0 | 22.0 |
| | ECM9 | 388.0 | 317.0 | 0.0 | 0.0 | 0.0 | 20.0 | 18.0 | 4.0 | NP |
| | ECM10 | 388.0 | 395.0 | 356.0 | 0.0 | 0.0 | 19.0 | 15.0 | 16.0 | 10.0 |
| LNMRC | ECG1 | 327 | 125 | 0.0 | 0.0 | 0.0 | ND | | | |
| | ECG2 | 451 | 421 | 320 | 240 | 0.0 | | | | |
| | ECG3 | 355 | 375 | 320 | ND | ND [‡] | | | | |

ND: No data (missing); NP: Not performed. [†]Recorded LOA at 4.8 years, [‡]Recorded LOA ~4.5 Years

APPENDIX 7. ETEPLIRSEN PATIENTS EXTERNAL CONTROL WITH RESULTS OF 6MWT AT YEAR 4

Study 201/202 Subjects (N = 12) with Results of 6MWT at Year 4

| Patient Number | Baseline 6MWT | Year 3 6MWT | Year 4 6MWT | Age at Year 4 |
|----------------|---------------|-------------|-------------|---------------|
| 012 | 351 | 298 | 237 | 14.6 |
| 013 | 400 | 301 | 230 | 14.3 |
| 008 | 346 | 100 | 55 | 14.2 |
| 006 | 355 | 359 | 332 | 14.2 |
| 010 | 256 | 0 | 0 | 13.5 |
| 009 | 330 | 0 | 0 | 13.5 |
| 015 | 401 | 483 | 400 | 13.3 |
| 002 | 416 | 378 | 349 | 12.7 |
| 004 | 389 | 355 | 221 | 12.5 |
| 007 | 374 | 312 | 197 | 11.7 |
| 005 | 374 | 247 | 143 | 11.7 |
| 003 | 366 | 324 | 192 | 11.0 |

Note: Patients 009 and 010 both lost ambulation at age 10.5

External Control Subjects (N = 13) with Results of 6MWT at Year 4

| Patient Number | Baseline 6MWT | Year 3 6MWT | Year 4 6MWT | Age at Year 4 | Age at LOA |
|----------------|---------------|-------------|------------------|---------------|------------|
| ECM2** | 380 | 195 | *Missing | 12.6 | 13.1‡ |
| ECM5 | 295 | 35 | 0 | 13.3 | 13.3 |
| ECM6 | 380 | 0 | 0 | 12.0 | 11 |
| ECM4 | 329 | 218 | 0 | 12.8 | 12.8 |
| ECM10 | 388 | 0 | 0 | 12.1 | 11.1 |
| ECM9 | 388 | 0 | 0 | 14.1 | 12.1 |
| ECM7 | 325 | 0 | 0 | 11.3 | 10.3 |
| ECM8 | 458 | 362 | 300 [†] | 14.2 | 15‡ |
| ECM1 | 200 | 0 | 0 | 15.5 | 13.5 |
| ECM3 | 373 | 273 | 0 | 13.0 | 13 |
| ECG1 | 327 | 0 | 0 | 15.5 | 13.8 |
| ECG2 | 451 | 240 | 0 | 15.2 | 15.5 |
| ECG3* | 355 | Missing | * Missing | 12.3 | 12.8‡ |

Note: External Control patients ECM2 and ECG3 were missing 6MWT data at Year 4. Of note, these patients were subsequently reported to have loss of ambulation with “0” meters on the 6MWT at ~4.5 years.

†External Control Patient ECM8 walked 300m on 6MWT at Year 4, and was subsequently reported to have loss of ambulation at 4.8 years.

‡LOA after year 4

APPENDIX 8. SENSITIVITY ANALYSIS FOR 6MWT ETEPLIRSEN-TREATED VS. EXTERNAL CONTROLS

Sensitivity Analyses to Control for Potential Group Imbalances in Important Baseline Prognostic Factors

The pre-specified primary ANCOVA analysis included baseline 6MWT as a covariate to control for potential imbalances between the groups (treated vs. untreated) in baseline 6MWT distance, an important prognostic factor for loss of ambulation. When age, another important predictor of 6MWT was added as a covariate to the same analysis, the difference between the eteplirsen-treated patients and untreated external controls remained clinically and statistically significant (Row 1). Additional ANCOVA models were performed where baseline steroid schedule (row 2), age at start of steroid and baseline age (row 3), baseline rise time (row 11), baseline height (row 12), and baseline weight (row 13). The difference remained clinically and statistically significant for all analyses.

Sensitivity Analyses to Account for Potential Violations of the Data's Normality Assumption

To address potential violations of Normality Assumption, the changes from baseline in 6MWT distance for all patients ($N = 12 + 13 = 25$) were ranked 1-25. Then the rank scores, which are not affected by large changes in 6MWT scores, were analyzed using ANCOVA. Two ANCOVA models were performed, the first included baseline 6MWT as a covariate (Row 4) and the second included both baseline 6MWT and age as covariates (Row 5). For both analyses, the difference between the eteplirsen-treated patients and untreated external controls remained statistically significant.

Sensitivity Analyses for Missing Data

One patient in the external control cohort ($N = 13$) did not contribute data through Year 4. To account for any potential bias caused by this approach, a series of Mixed Model Repeated Measures (MMRM) analyses were performed to control for potential bias caused by missing data at later time points. The MMRM analysis uses all available data (i.e., Years 1, 2, 3 and 4) to estimate the data's correlation structure between time points, thereby reducing the impact of missing data without explicit imputation. An AR(1) covariance structure was assigned. Two MMRMs were performed. The first included both baseline 6MWT and age as covariates (Row 6), and the second was an MMRM analysis of the rank-transformed data, with both baseline 6MWT and age as covariates (Row 7). For both of these analyses, the difference between the eteplirsen treated patients and untreated external controls remained statistically significant.

Additionally, a series of sensitivity analyses were conducted in which the last observed value for the patient at 3.5 years (225 meters) was imputed as the 48 month result (last observation carried forward or LOCF). This is a highly conservative approach as the patient would not be expected to remain stable over this period of time given his age at baseline (8.6 years). Two different ANCOVAs were performed using LOCF for missing data. The first included baseline 6MWT as a covariate (Row 8), the second included both baseline 6MWT and age as covariates (Row 9).

Even with these most conservative analyses, the difference between the eteplirsen-treated and untreated external control patients remained statistically significant.

APPENDIX 9. INDIVIDUAL ITEMS OF NSAA

1. Stand
 2. Walk
 3. Stand from chair
 4. Stand R leg
 5. Stand L leg
 6. Climb R leg
 7. Climb L leg
 8. Descend R leg
 9. Descend L leg
 10. Gets to sitting
 11. Rise from floor
 12. Lifts head
 13. Stands on heels
 14. Jump
 15. Hop R leg
 16. Hop L leg
 17. Run
- Total score

**APPENDIX 10. UNTREATED CONTROL MUSCLE BIOPSY SAMPLES
 USED IN WEEK 180 DYSTROPHIN ANALYSIS**

| Sample ID | Age (age at biopsy years) | Anatomical Location | Dystrophin Mutation | Baseline 6MWT | Source |
|-----------|---------------------------------|------------------------|------------------------|------------------|-----------|
| 01005 | 7 | Biceps | $\Delta 50$ | 357 m | Study 201 |
| 01008 | 10 | Biceps | $\Delta 49-50$ | 341 m | |
| 01013 | 10 | Biceps | $\Delta 45-50$ | 418 m | |
| 01015 | 9 | Biceps | $\Delta 52$ | 401 m | |
| DMD #1 | 7 | Deltoid | $\Delta 45-50$ | 425 m | Study 301 |
| DMD #2 | 8 | Biceps | $\Delta 45-50$ | 421 m | |
| DMD #3 | 15 | Biceps | $\Delta 48-50$ | 352 m | |
| DMD #4 | 7 | Biceps | $\Delta 45-50$ | 402 m | |
| DMD #5 | 10 | Biceps | $\Delta 50$ | 538 m | |
| DMD #6 | 7 | Biceps | $\Delta 49-50$ | 383 m | |
| DMD #7 | 9 | Biceps | $\Delta 49-50$ | 441 m | |
| DMD #8 | 9 | Biceps | $\Delta 48-50$ | 306 m | |
| DMD #9 | 9 | Biceps | $\Delta 52$ | 371 m | |

**APPENDIX 11. INDIVIDUAL PATIENT RESULTS FOR PERCENT
 DYSTROPHIN POSITIVE FIBERS (PDPF)**

| Patient ID | Multi-rater PDPF % | |
|------------|--------------------|-----------------------|
| | Week 180 | Baseline ¹ |
| 01002 | 4.54 | -- |
| 01003 | 1.42 | -- |
| 01004 | 28.2 | -- |
| 01006 | 20.72 | -- |
| 01007 | 7.08 | -- |
| 01008 | 12.75 | 1.09 |
| 01009 | 21.48 | -- |
| 01010 | 23.96 | -- |
| 01012 | 33.5 | -- |
| 01013 | 19.14 | 2.58 |
| 01015 | 18.48 | 0.19 |

¹ Baseline muscle biopsy tissue was not available for most patients. For patients where it was available, baseline analysis was performed on the archived tissue using updated methodology coincident with Week 180 analysis.

| Patient ID | Multi-rater PDPF % Untreated |
|------------|------------------------------|
| DMD1 | 0.15 |
| DMD2 | 0.29 |
| DMD3 | 3.95 |
| DMD4 | 0.39 |
| DMD5 | 0.36 |
| DMD6 | 1.11 |

APPENDIX 12. INDIVIDUAL PATIENT RESULTS FOR DYSTROPHIN FIBER INTENSITY

| Patient ID | Fiber Intensity % | |
|------------|-------------------|-----------------------|
| | Week 180 | Baseline ¹ |
| 01003 | 7.0 | -- |
| 01004 | 28.8 | -- |
| 01006 | 28.7 | -- |
| 01007 | 12.0 | -- |
| 01008 | 26.7 | 11.6 |
| 01009 | 23.0 | -- |
| 01010 | 21.4 | -- |
| 01012 | 26.1 | -- |
| 01013 | 32.5 | 16.3 |
| 01015 | 30.7 | 7.4 |

¹ Baseline muscle biopsy tissue was not available for most patients. For patients where it was available, baseline analysis was performed on the archived tissue using updated methodology coincident with Week 180 analysis.

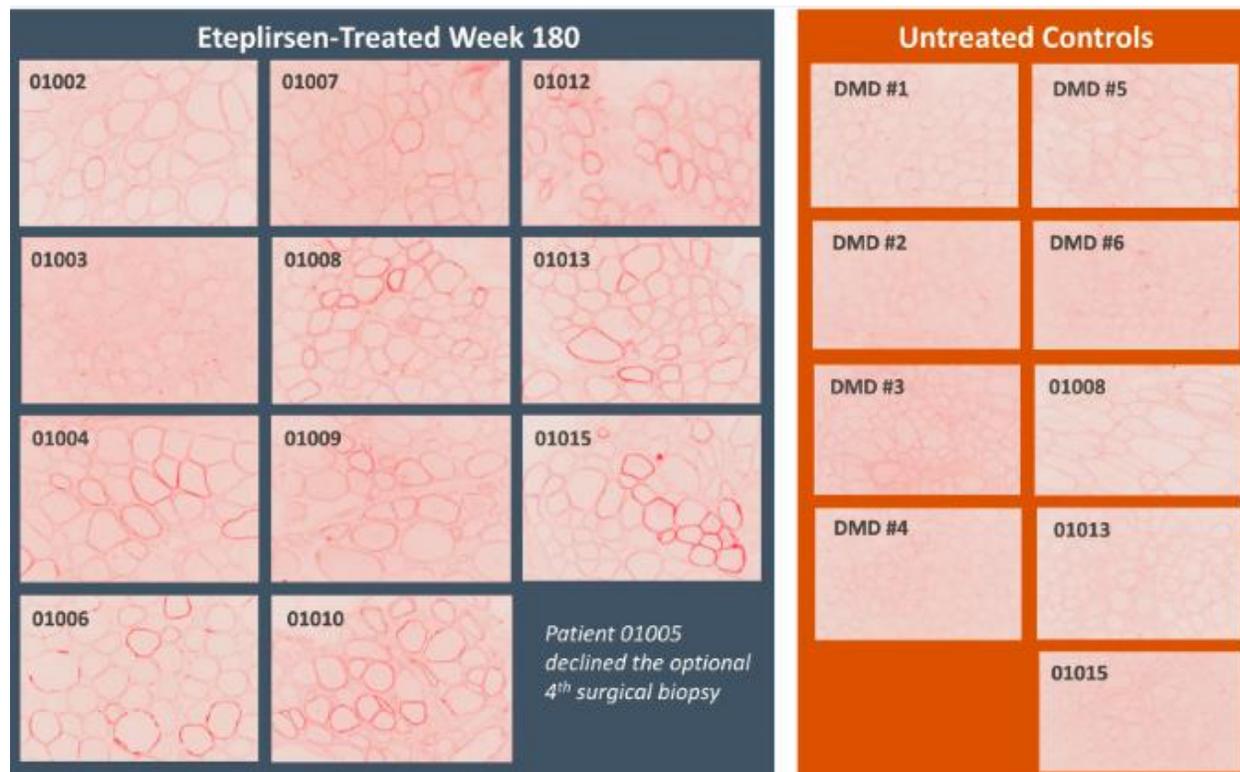
| Patient ID | Fiber Intensity % Untreated |
|------------|-----------------------------|
| DMD1 | 9.9 |
| DMD2 | 6.1 |
| DMD3 | 9.2 |
| DMD4 | 3.5 |
| DMD5 | 17.6 |
| DMD6 | 3.1 |

APPENDIX 13. DIGITAL MICROSCOPY IMAGES FOR ASSESSMENT OF PERCENT POSITIVE DYSTROPHIN FIBERS

Muscle biopsy cryosections were immunostained with monoclonal antibody MANDYS106 by indirect immunofluorescence. Fluorescence microscope digital images were captured at 20X magnification. To more clearly display relative intensity of fibers, the contrast was inverted from original fluorescence images to display a pseudo-bright field image and the intensity enhanced for display purposes only in this figure. These enhanced images were not used in the analysis of figure intensity, nor to score dystrophin-positive fibers.

The enhanced inverted algorithm produces a non-linear mapping of r,g,b fluorescence values that will specifically enhance low contrast objects in the image. The degree of enhancement was consistent for all images, preserving the ability to visually compare relative intensity in the figures, below.

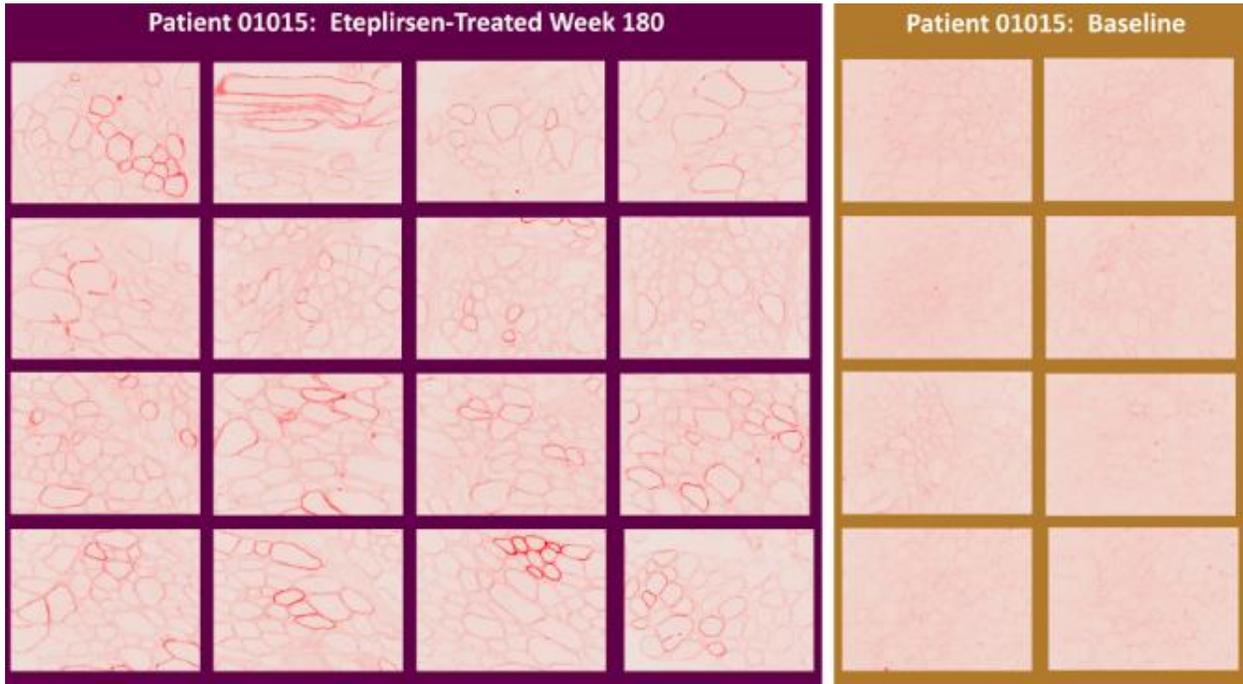
One image per patient is shown and for comparison, one image per DMD untreated control sample.



Images enhanced for display purposes only

All 16 images are shown that were analyzed for patient 01015 for muscle biopsy sample at Week 180 and at baseline. Systematic random sampling of image fields for each stained tissue section was used to capture four 20X images per tissue section. Tissue was sectioned at 2 levels from each of 2 distinct muscle biopsy samples, resulting in a total of 16 images per patient at Week 180 (4 images, 2 tissue levels, 2 biopsy samples) and 8 images at baseline (4 images, 2 tissue levels, 1 biopsy sample). As described above, to more clearly display relative intensity of fibers, the contrast was inverted from original fluorescence images to display a pseudo-bright

field image and the intensity enhanced for display purposes only in this figure. These enhanced images were not used in the analysis of fiber intensity, nor to score dystrophin-positive fibers.



Images enhanced for display purposes only

APPENDIX 14. INDIVIDUAL PATIENT RESULTS FOR WESTERN BLOT

| Patient ID | Western Blot % | |
|------------|-------------------|-----------------------|
| | Week 180 | Baseline ¹ |
| 002 | 0.14 ⁴ | -- |
| 003 | 0 (BLOQ) | -- |
| 004 | 0.96 | -- |
| 005 | n.a. ² | 0 (BLOQ) ³ |
| 006 | 2.47 | -- |
| 007 | 0 (BLOQ) | -- |
| 008 | 0.98 | -- |
| 009 | 0.52 | -- |
| 010 | 1.62 | -- |
| 012 | 0.38 | -- |
| 013 | 1.15 | 0 (BLOQ) |
| 015 | 2.05 | 0 (BLOQ) |

Abbreviations: BLOQ = Below Limit of Quantification

¹ Baseline muscle biopsy tissue was not available for most patients. For patients where it was available, baseline analysis was performed on the archived tissue using updated methodology coincident with Week 180 analysis.

² Patient 005 did not consent for fourth biopsy.

³ Baseline muscle biopsy tissue from patient 005 was used in Western blot assays as there was not sufficient tissue remaining from patient 008.

⁴ One of two replicate gels was above BLOQ of 0.25% while the other was below and treated as zero. The average of two gels is reported.

| Patient ID | Western Blot % Untreated |
|-------------------|-----------------------------|
| DMD1 | 0 (BLOQ) |
| DMD2 | 0 (BLOQ) |
| DMD3 | 0.37 |
| DMD7 ¹ | 0.15 ² |
| DMD8 ¹ | 0 (BLOQ) |
| DMD9 ¹ | 0.20 ² |

¹ Control DMD muscle biopsy tissue from DMD7, DMD8, DMD9 were used in Western blot assays as there was not sufficient tissue remaining from DMD4, DMD5, DMD6.

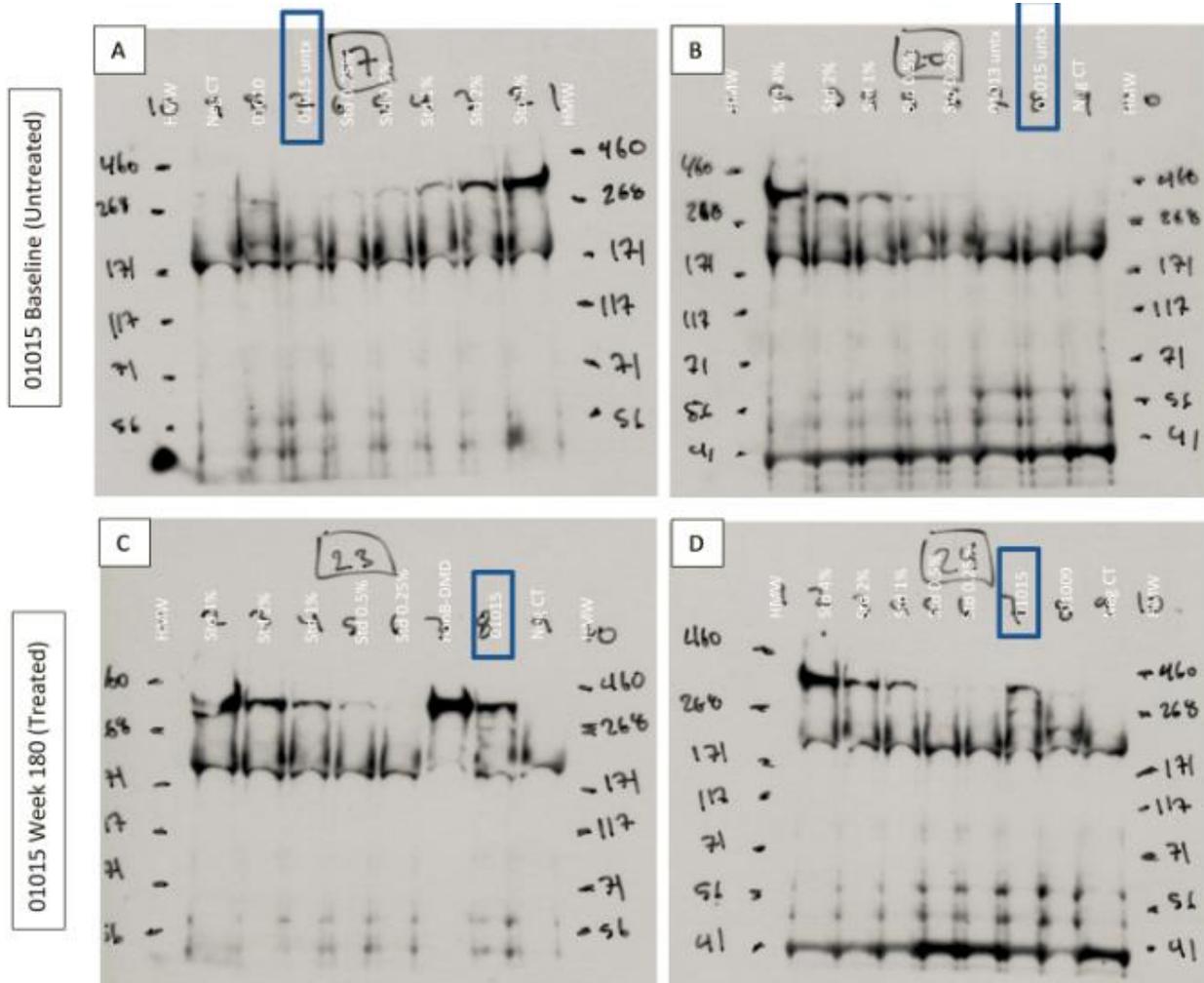
² One of two replicate gels was above BLOQ of 0.25% while the other gel was below and treated as zero. The average of two gels is reported.

APPENDIX 15. WESTERN BLOT ACCEPTANCE STANDARDS AND REPRESENTATIVE GEL IMAGES

All samples analyzed in the 4th biopsy by Western blot were run in duplicate on separate gels. NCL-DYS1 anti-dystrophin antibody was used to stain for dystrophin. A validated, sensitive method for Western blot was established with pass/fail criteria for each gel:

- 5-point standard curve (0.25%-4% of normal) included on every gel
 - Normal control muscle lysate spiked in DMD muscle lysate to control for equal muscle protein load in each lane
 - Lower limit of quantitation is 0.25% of normal muscle
 - Pass criteria of $R^2 > 0.90$ to ensure standard curve linearity on each gel
- Negative control included on every gel
 - DMD muscle lysate used for standard curve (without normal control muscle lysate)
 - False positive reads prevented by setting gel pass criteria for negative lane density of $< 0.25\%$ lane density to control
- Samples run blinded in duplicate on separate gels
- Alpha-actinin (muscle-specific protein expressed equally in DMD and non-DMD muscle tissue) used as control for equal protein load
 - Equal lane to lane protein load confirmed by pass criteria of $RSD < 50\%$ of average actinin density for all lanes

Western Blot Images of 4 Separate Gels Illustrating Dystrophin Absence in Pretreatment Muscle of Patient 01015 (A Lane 7 + B Lane 8) and *de novo* Dystrophin Protein Production After Eteplirsen Treatment at Week 180 in Tissue From the Same Patient 01015 (C Lane 8 + D Lane 7)



All gel images depicted here were obtained with a 30 minute exposure. All lanes (excluding high molecular weight lanes) were loaded with a consistent 50µg total protein load. Alpha-actinin, a muscle specific protein expressed equally in DMD and non-DMD muscle tissue, was used as a loading control to ensure equal protein load (not depicted here).

**APPENDIX 16. ALL TREATMENT-EMERGENT ADVERSE EVENTS
DURING THE 24-WEEK PLACEBO CONTROL
PERIOD OF STUDY 201**

| System Organ Classification Preferred Term | Eteplirsen | | | |
|--|-------------------------|-----------------------------|-----------------------------|-----------------------------------|
| | Placebo (N = 4) n | 30 mg/kg/wk (N = 4) n | 50 mg/kg/wk (N = 4) n | All Eteplirsen (N = 8) n |
| At Least One TEAE | 4 | 4 | 4 | 8 |
| Injury, poisoning & procedural complications | 4 | 3 | 4 | 7 |
| Procedural pain | 3 | 1 | 3 | 4 |
| Fall | 1 | 1 | 0 | 1 |
| Incision site pain | 1 | 1 | 0 | 1 |
| Arthropod bite | 0 | 1 | 0 | 1 |
| Back injury | 0 | 1 | 0 | 1 |
| Foot fracture | 0 | 0 | 1 | 1 |
| Joint injury | 0 | 1 | 0 | 1 |
| Wound dehiscence | 1 | 0 | 0 | 0 |
| Respiratory, thoracic & mediastinal disorders | 3 | 4 | 1 | 5 |
| Oropharyngeal pain | 3 | 3 | 0 | 3 |
| Cough | 2 | 1 | 1 | 2 |
| Nasal congestion | 2 | 1 | 0 | 1 |
| Sinus congestion | 0 | 1 | 0 | 1 |
| Upper respiratory tract congestion | 0 | 1 | 0 | 1 |
| Musculoskeletal & connective tissue disorders | 3 | 2 | 2 | 4 |
| Pain in extremity | 3 | 0 | 1 | 1 |
| Back pain | 2 | 1 | 0 | 1 |
| Arthralgia | 0 | 0 | 1 | 1 |
| Bone pain | 0 | 1 | 0 | 1 |
| Muscle spasms | 0 | 0 | 1 | 1 |
| Musculoskeletal pain | 0 | 1 | 0 | 1 |
| Nervous system disorders | 2 | 3 | 2 | 5 |
| Balance disorder | 0 | 1 | 2 | 3 |
| Headache | 2 | 1 | 0 | 1 |
| Dizziness | 1 | 0 | 0 | 0 |

| System Organ Classification Preferred Term | Eteplirsen | | | |
|---|-------------------------|-----------------------------|-----------------------------|-----------------------------------|
| | Placebo (N = 4) n | 30 mg/kg/wk (N = 4) n | 50 mg/kg/wk (N = 4) n | All Eteplirsen (N = 8) n |
| At Least One TEAE | 4 | 4 | 4 | 8 |
| Somnolence | 0 | 1 | 0 | 1 |
| General disorders and administration site conditions | 2 | 2 | 2 | 4 |
| Pyrexia | 2 | 1 | 0 | 1 |
| Injection site pain | 0 | 0 | 1 | 1 |
| Malaise | 0 | 0 | 1 | 1 |
| Non-cardiac chest pain | 0 | 1 | 0 | 1 |
| Pain | 0 | 0 | 1 | 1 |
| Metabolism & nutrition disorders | 2 | 2 | 2 | 4 |
| Hypokalaemia | 2 | 2 | 2 | 4 |
| Gastrointestinal disorders | 2 | 1 | 2 | 3 |
| Vomiting | 0 | 1 | 2 | 3 |
| Abdominal pain | 2 | 0 | 0 | 0 |
| Diarrhoea | 1 | 0 | 1 | 1 |
| Nausea | 1 | 0 | 1 | 1 |
| Infections & infestations | 3 | 0 | 1 | 1 |
| Rhinitis | 1 | 0 | 1 | 1 |
| Enterobiasis | 1 | 0 | 0 | 0 |
| Nasopharyngitis | 1 | 0 | 0 | 0 |
| Soft tissue infection | 1 | 0 | 0 | 0 |
| Vascular disorders | 1 | 1 | 1 | 2 |
| Haematoma | 1 | 1 | 1 | 2 |
| Renal & urinary disorders | 1 | 1 | 0 | 1 |
| Polyuria | 0 | 1 | 0 | 1 |
| Proteinuria | 1 | 0 | 0 | 0 |
| Skin & subcutaneous tissue disorders | 0 | 2 | 0 | 2 |
| Dermatitis contact | 0 | 2 | 0 | 2 |
| Petechiae | 0 | 1 | 0 | 1 |
| Urticaria thermal | 0 | 1 | 0 | 1 |
| Cardiac disorders | 0 | 1 | 0 | 1 |

| System Organ Classification Preferred Term | Eteplirsen | | | |
|---|-------------------------|-----------------------------|-----------------------------|-----------------------------------|
| | Placebo (N = 4) n | 30 mg/kg/wk (N = 4) n | 50 mg/kg/wk (N = 4) n | All Eteplirsen (N = 8) n |
| At Least One TEAE | 4 | 4 | 4 | 8 |
| Tachycardia | 0 | 1 | 0 | 1 |
| Ear & labyrinth disorders | 0 | 0 | 1 | 1 |
| Motion sickness | 0 | 0 | 1 | 1 |

Note: AEs are coded using MedDRA v14.0. AEs were attributed to the treatment being received at start of AE. TEAEs are those starting during or after the first infusion of study drug. Patients who experience a coded event more than once are only counted once per treatment received.

APPENDIX 17. TREATMENT-EMERGENT ADVERSE EVENTS DURING THE ETEPLIRSEN CLINICAL DEVELOPMENT PROGRAM

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|---|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Number of Subjects With a TEAE | 4 (100%) | 9 (60.0%) | 5 (71.4%) | 11 (100%) | 4 (100%) | 4 (100%) | 63 (76.8%) | 6 (100%) | 88 (82.2%) | 93 (81.6%) |
| Injury, poisoning and procedural complications | 4 (100%) | 3 (20.0%) | 0 | 9 (81.8%) | 1 (25.0%) | 1 (25.0%) | 33 (40.2%) | 6 (100%) | 50 (46.7%) | 50 (43.9%) |
| Procedural pain | 3 (75.0%) | 0 | 0 | 2 (18.2%) | 0 | 0 | 8 (9.8%) | 6 (100%) | 16 (15.0%) | 16 (14.0%) |
| Contusion | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 10 (12.2%) | 3 (50.0%) | 14 (13.1%) | 14 (12.3%) |
| Excoriation | 0 | 0 | 0 | 0 | 0 | 1 (25.0%) | 11 (13.4%) | 2 (33.3%) | 14 (13.1%) | 14 (12.3%) |
| Fall | 1 (25.0%) | 0 | 0 | 4 (36.4%) | 0 | 0 | 7 (8.5%) | 0 | 11 (10.3%) | 11 (9.6%) |
| Arthropod bite | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 5 (6.1%) | 1 (16.7%) | 7 (6.5%) | 7 (6.1%) |
| Incision site haemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Joint injury | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Joint sprain | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 1 (1.2%) | 3 (50.0%) | 4 (3.7%) | 4 (3.5%) |
| Foot fracture | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Head injury | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Muscle strain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 2 (33.3%) | 3 (2.8%) | 3 (2.6%) |
| Post procedural haematoma | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Arthropod sting | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Limb injury | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Scratch | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Thermal burn | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Accident | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Ankle fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Back injury | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Burns first degree | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Femur fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Hand fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Heat stroke | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Incision site erythema | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Incision site pain | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Incision site pruritus | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Infusion related reaction | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Laceration | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Ligament sprain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Lip injury | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Lower limb fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Nail injury | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Radius fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Skeletal injury | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Soft tissue injury | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Spinal compression fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Sunburn | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Tooth fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Wound dehiscence | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tooth avulsion | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Torus fracture | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|------------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Gastrointestinal disorders | 1 (25.0%) | 2 (13.3%) | 0 | 8 (72.7%) | 1 (25.0%) | 2 (50.0%) | 27 (32.9%) | 5 (83.3%) | 43 (40.2%) | 43 (37.7%) |
| Vomiting | 0 | 0 | 0 | 2 (18.2%) | 1 (25.0%) | 0 | 18 (22.0%) | 3 (50.0%) | 24 (22.4%) | 24 (21.1%) |
| Nausea | 1 (25.0%) | 0 | 0 | 2 (18.2%) | 0 | 1 (25.0%) | 4 (4.9%) | 2 (33.3%) | 9 (8.4%) | 9 (7.9%) |
| Abdominal pain upper | 0 | 1 (6.7%) | 0 | 2 (18.2%) | 0 | 0 | 3 (3.7%) | 3 (50.0%) | 8 (7.5%) | 8 (7.0%) |
| Abdominal pain | 1 (25.0%) | 0 | 0 | 2 (18.2%) | 0 | 0 | 3 (3.7%) | 2 (33.3%) | 7 (6.5%) | 7 (6.1%) |
| Diarrhoea | 0 | 1 (6.7%) | 0 | 1 (9.1%) | 0 | 0 | 4 (4.9%) | 2 (33.3%) | 7 (6.5%) | 7 (6.1%) |
| Dyspepsia | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Constipation | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 2 (33.3%) | 3 (2.8%) | 3 (2.6%) |
| Abdominal discomfort | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Haematochezia | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Abdominal distension | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Dental caries | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Dysphagia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Flatulence | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Food poisoning | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Haemorrhoids | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Lip dry | 0 | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Lip swelling | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Oral pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Retained deciduous tooth | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tooth impacted | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Toothache | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|---|------------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Musculoskeletal and connective tissue disorders | 3 (75.0%) | 2 (13.3%) | 0 | 8 (72.7%) | 1 (25.0%) | 0 | 28 (34.1%) | 6 (100%) | 43 (40.2%) | 43 (37.7%) |
| Back pain | 2 (50.0%) | 0 | 0 | 3 (27.3%) | 1 (25.0%) | 0 | 17 (20.7%) | 3 (50.0%) | 24 (22.4%) | 24 (21.1%) |
| Pain in extremity | 3 (75.0%) | 0 | 0 | 2 (18.2%) | 1 (25.0%) | 0 | 10 (12.2%) | 4 (66.7%) | 17 (15.9%) | 17 (14.9%) |
| Arthralgia | 0 | 0 | 0 | 3 (27.3%) | 0 | 0 | 8 (9.8%) | 3 (50.0%) | 14 (13.1%) | 14 (12.3%) |
| Muscle spasms | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 2 (33.3%) | 5 (4.7%) | 5 (4.4%) |
| Myalgia | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 2 (2.4%) | 2 (33.3%) | 5 (4.7%) | 5 (4.4%) |
| Musculoskeletal pain | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Muscular weakness | 0 | 2 (13.3%) | 0 | 0 | 0 | 0 | 1 (1.2%) | 2 (33.3%) | 3 (2.8%) | 3 (2.6%) |
| Coccydynia | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 1 (1.2%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Neck pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Tendonitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Bone pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Groin pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Joint swelling | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Osteopenia | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Scoliosis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tendinous contracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tendon disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| General Disorders and Administration Site Conditions | 2 (50.0%) | 0 | 2 (28.6%) | 3 (27.3%) | 2 (50.0%) | 2 (50.0%) | 23 (28.0%) | 5 (83.3%) | 35 (32.7%) | 37 (32.5%) |
| Catheter site pain | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 7 (8.5%) | 2 (33.3%) | 10 (9.3%) | 10 (8.8%) |
| Infusion site haematoma | 0 | 0 | 0 | 0 | 0 | 0 | 6 (7.3%) | 1 (16.7%) | 7 (6.5%) | 7 (6.1%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Fatigue | 0 | 0 | 0 | 1 (9.1%) | 1 (25.0%) | 0 | 4 (4.9%) | 0 | 6 (5.6%) | 6 (5.3%) |
| Catheter site haematoma | 0 | 0 | 0 | 2 (18.2%) | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Infusion site extravasation | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 2 (33.3%) | 4 (3.7%) | 4 (3.5%) |
| Pyrexia | 2 (50.0%) | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 2 (33.3%) | 4 (3.7%) | 4 (3.5%) |
| Influenza like illness | 0 | 0 | 0 | 1 (9.1%) | 1 (25.0%) | 0 | 1 (1.2%) | 0 | 3 (2.8%) | 3 (2.6%) |
| Infusion site pain | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Thrombosis in device | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 0 | 3 (2.8%) | 3 (2.6%) |
| Chest pain | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 1 (1.2%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Device occlusion | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Disease progression | 0 | 0 | 0 | 0 | 1 (25.0%) | 1 (25.0%) | 0 | 0 | 2 (1.9%) | 2 (1.8%) |
| Injection site pain | 0 | 0 | 1 (14.3%) | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 2 (1.8%) |
| Non-cardiac chest pain | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Oedema peripheral | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Application site erythema | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Application site rash | 0 | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Catheter site haemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Catheter site inflammation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Catheter site related reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Feeling hot | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Gait disturbance | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Infusion site rash | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Infusion site swelling | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Injection site haematoma | 0 | 0 | 1 (14.3%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|------------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Irritability | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Malaise | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Swelling | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Vaccination site pain | 0 | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Infections and infestations | 3 (75.0%) | 2 (13.3%) | 0 | 5 (45.5%) | 4 (100%) | 2 (50.0%) | 19 (23.2%) | 6 (100%) | 36 (33.6%) | 36 (31.6%) |
| Upper respiratory tract infection | 0 | 0 | 0 | 3 (27.3%) | 2 (50.0%) | 1 (25.0%) | 5 (6.1%) | 4 (66.7%) | 15 (14.0%) | 15 (13.2%) |
| Nasopharyngitis | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 10 (12.2%) | 4 (66.7%) | 14 (13.1%) | 14 (12.3%) |
| Rhinitis | 1 (25.0%) | 0 | 0 | 1 (9.1%) | 3 (75.0%) | 1 (25.0%) | 0 | 1 (16.7%) | 6 (5.6%) | 6 (5.3%) |
| Ear infection | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 0 | 3 (2.8%) | 3 (2.6%) |
| Gastroenteritis viral | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Hordeolum | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 2 (33.3%) | 3 (2.8%) | 3 (2.6%) |
| Viral infection | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Gastroenteritis | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Influenza | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (33.3%) | 2 (1.9%) | 2 (1.8%) |
| Pharyngitis streptococcal | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Post procedural cellulitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Body tinea | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Bronchitis | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Candidiasis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Folliculitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Furuncle | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Incision site infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|------------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Sinusitis | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Skin infection | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tinea infection | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Tinea pedis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tooth abscess | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Tooth infection | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Viral upper respiratory tract infection | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Enterobiasis | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphadenitis viral | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Otitis media | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Soft tissue infection | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nervous system disorders | 2 (50.0%) | 1 (6.7%) | 0 | 6 (54.5%) | 2 (50.0%) | 2 (50.0%) | 20 (24.4%) | 6 (100%) | 36 (33.6%) | 36 (31.6%) |
| Headache | 2 (50.0%) | 1 (6.7%) | 0 | 5 (45.5%) | 2 (50.0%) | 1 (25.0%) | 14 (17.1%) | 5 (83.3%) | 27 (25.2%) | 27 (23.7%) |
| Dizziness | 1 (25.0%) | 0 | 0 | 2 (18.2%) | 0 | 1 (25.0%) | 3 (3.7%) | 0 | 6 (5.6%) | 6 (5.3%) |
| Balance disorder | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 3 (50.0%) | 5 (4.7%) | 5 (4.4%) |
| Paraesthesia | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Psychomotor hyperactivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Somnolence | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Respiratory, thoracic and mediastinal disorders | 3 (75.0%) | 1 (6.7%) | 0 | 2 (18.2%) | 0 | 0 | 28 (34.1%) | 6 (100%) | 36 (33.6%) | 36 (31.6%) |
| Cough | 2 (50.0%) | 0 | 0 | 2 (18.2%) | 0 | 0 | 12 (14.6%) | 4 (66.7%) | 18 (16.8%) | 18 (15.8%) |
| Oropharyngeal pain | 3 (75.0%) | 0 | 0 | 0 | 0 | 0 | 10 (12.2%) | 4 (66.7%) | 14 (13.1%) | 14 (12.3%) |
| Nasal congestion | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 11 (13.4%) | 2 (33.3%) | 13 (12.1%) | 13 (11.4%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|---|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Rhinorrhoea | 0 | 0 | 0 | 0 | 0 | 0 | 5 (6.1%) | 2 (33.3%) | 7 (6.5%) | 7 (6.1%) |
| Epistaxis | 0 | 0 | 0 | 0 | 0 | 0 | 4 (4.9%) | 1 (16.7%) | 5 (4.7%) | 5 (4.4%) |
| Pharyngeal erythema | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Upper respiratory tract congestion | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Productive cough | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Respiratory disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Sinus congestion | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Sneezing | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Upper-airway cough syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Skin and Subcutaneous Tissue Disorders | 0 | 1 (6.7%) | 0 | 1 (9.1%) | 0 | 1 (25.0%) | 20 (24.4%) | 5 (83.3%) | 27 (25.2%) | 27 (23.7%) |
| Rash | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 9 (11.0%) | 1 (16.7%) | 10 (9.3%) | 10 (8.8%) |
| Dermatitis contact | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Ecchymosis | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Erythema | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Papule | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Rash papular | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Acne | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Alopecia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Dermatitis bullous | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Drug eruption | 0 | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Ingrowing nail | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|---|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Intertrigo | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Keloid scar | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Nail discolouration | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Nail dystrophy | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Petechiae | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Rash pruritic | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Skin erosion | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Skin hyperpigmentation | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Skin irritation | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Urticaria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Urticaria thermal | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Investigations | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 12 (14.6%) | 6 (100%) | 18 (16.8%) | 18 (15.8%) |
| Activated partial thromboplastin time prolonged | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 3 (50.0%) | 5 (4.7%) | 5 (4.4%) |
| C-reactive protein increased | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 2 (33.3%) | 5 (4.7%) | 5 (4.4%) |
| Blood creatine phosphokinase increased | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Blood glucose increased | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Body height below normal | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Protein urine present | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Blood amylase increased | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Blood creatinine increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Blood urea increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|------------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Blood urine present | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Breath sounds abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Lymphocyte count decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Neutrophil count increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Red blood cells urine positive | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Urine analysis abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Urine ketone body present | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| White blood cell count decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Wound healing normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Influenza A virus test positive | 0 | 1 (6.7%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal and Urinary Disorders | 1 (25.0%) | 0 | 3 (42.9%) | 0 | 0 | 1 (25.0%) | 7 (8.5%) | 4 (66.7%) | 12 (11.2%) | 15 (13.2%) |
| Proteinuria | 1 (25.0%) | 0 | 0 | 0 | 0 | 0 | 5 (6.1%) | 4 (66.7%) | 9 (8.4%) | 9 (7.9%) |
| Myoglobinuria | 0 | 0 | 3 (42.9%) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (2.6%) |
| Chromaturia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Crystalluria | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Enuresis | 0 | 0 | 0 | 0 | 0 | 1 (25.0%) | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Glycosuria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Hypercalciuria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Polyuria | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Urine odour abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|------------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|-------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Metabolism and Nutrition Disorders | 2 (50.0%) | 0 | 0 | 1 (9.1%) | 0 | 0 | 7 (8.5%) | 3 (50.0%) | 11 (10.3%) | 11 (9.6%) |
| Decreased appetite | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 3 (3.7%) | 0 | 4 (3.7%) | 4 (3.5%) |
| Hypokalaemia | 2 (50.0%) | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 2 (33.3%) | 4 (3.7%) | 4 (3.5%) |
| Dehydration | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Obesity | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Vitamin D deficiency | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Psychiatric Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 10 (12.2%) | 1 (16.7%) | 11 (10.3%) | 11 (9.6%) |
| Aggression | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Anxiety | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Insomnia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 (16.7%) | 2 (1.9%) | 2 (1.8%) |
| Antisocial behaviour | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Anxiety disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Bruxism | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Euphoric mood | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Mood altered | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Sleep disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Vascular Disorders | 1 (25.0%) | 0 | 0 | 2 (18.2%) | 0 | 1 (25.0%) | 4 (4.9%) | 1 (16.7%) | 8 (7.5%) | 8 (7.0%) |
| Haematoma | 1 (25.0%) | 0 | 0 | 1 (9.1%) | 0 | 1 (25.0%) | 1 (1.2%) | 1 (16.7%) | 4 (3.7%) | 4 (3.5%) |
| Flushing | 0 | 0 | 0 | 0 | 0 | 0 | 3 (3.7%) | 0 | 3 (2.8%) | 3 (2.6%) |
| Pallor | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Cardiac Disorders | 0 | 0 | 1 (14.3%) | 1 (9.1%) | 0 | 2 (50.0%) | 2 (2.4%) | 0 | 5 (4.7%) | 6 (5.3%) |
| Tachycardia | 0 | 0 | 0 | 1 (9.1%) | 0 | 2 (50.0%) | 1 (1.2%) | 0 | 4 (3.7%) | 4 (3.5%) |
| Cardiomyopathy | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |

| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | | |
|--|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|------------------|--------------------------|-----------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) | |
| Congestive cardiomyopathy | 0 | 0 | 1 (14.3%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) |
| Cardiac fibrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Sinus tachycardia | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Ear and Labyrinth Disorders | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 1 (1.2%) | 2 (33.3%) | 4 (3.7%) | 4 (3.5%) |
| Cerumen impaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Ear pain | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Motion sickness | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Tympanic membrane disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Eye Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 2 (33.3%) | 3 (2.8%) | 3 (2.6%) |
| Cataract | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Cataract subcapsular | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Conjunctivitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Erythema of eyelid | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Hypermetropia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Immune System Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 1 (16.7%) | 3 (2.8%) | 3 (2.6%) |
| Seasonal allergy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Hypersensitivity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Endocrine Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (33.3%) | 2 (1.9%) | 2 (1.8%) |
| Goitre | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Growth hormone deficiency | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |

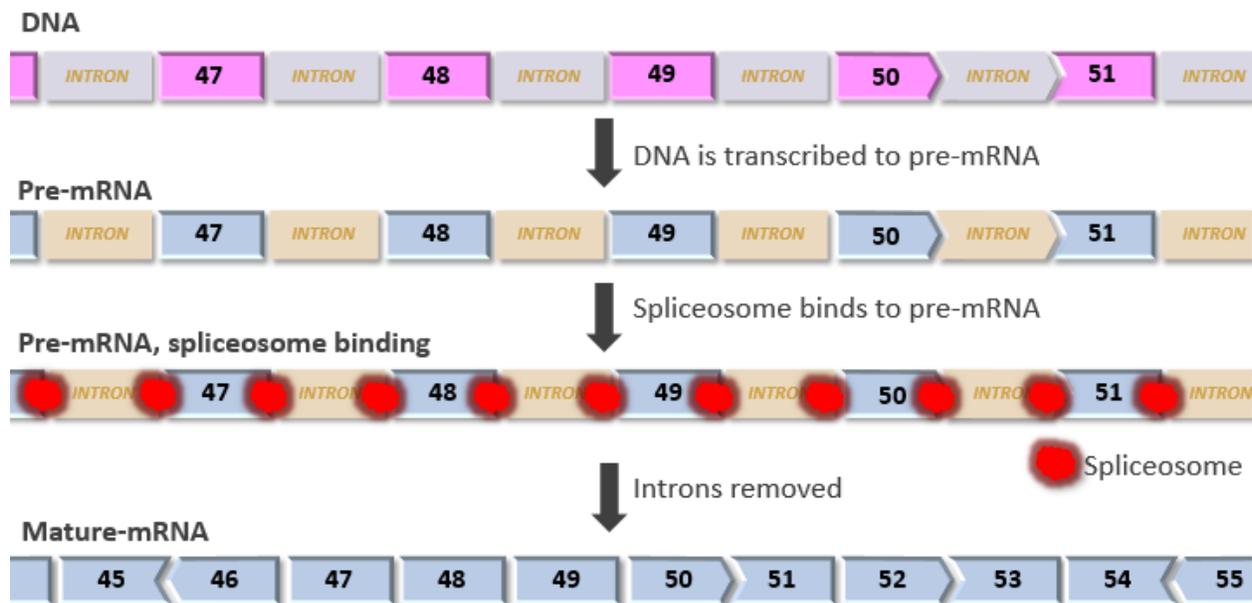
| System Organ Classification Preferred Term | Placebo (N = 4) | Untreated (N = 15) | Eteplirsen | | | | | | | |
|--|-----------------|--------------------|--------------------------|----------------------|---------------------|---------------------|----------------------|---------------------|------------------|--------------------------|
| | | | 0.09 & 0.9 mg IM (N = 7) | ≤4 mg/kg IV (N = 11) | 10 mg/kg IV (N = 4) | 20 mg/kg IV (N = 4) | 30 mg/kg IV (N = 82) | 50 mg/kg IV (N = 6) | All IV (N = 107) | All Eteplirsen (N = 114) |
| Reproductive System and Breast Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 | 2 (1.9%) | 2 (1.8%) |
| Pelvic pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Testicular pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Blood and Lymphatic System Disorders | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Platelet anisocytosis | 0 | 0 | 0 | 1 (9.1%) | 0 | 0 | 0 | 0 | 1 (0.9%) | 1 (0.9%) |
| Congenital, Familial, and Genetic Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Cryptorchism | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.9%) | 1 (0.9%) |
| Neoplasms Benign, Malignant, and Unspecified (Incl. Cysts and Polyps) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |
| Skin papilloma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7%) | 1 (0.9%) | 1 (0.9%) |

APPENDIX 18. DMD, EXON SKIPPING AND ETEPLIRSEN MECHANISM OF ACTION

Central Dogma of Molecular Biology, Introns & Exons

Watson and Crick’s proposed use of DNA by the cell, that is DNA is transcribed into RNA and then RNA is translated into protein, has been further elucidated to include the removal of introns from RNA prior to translation into protein. DNA and the pre-mRNA that is a direct copy of DNA contain both introns and exons. As shown in Figure A, the introns are removed from the pre-mRNA by protein complexes called spliceosomes to create the final, mature mRNA that is translated by the ribosome into protein.

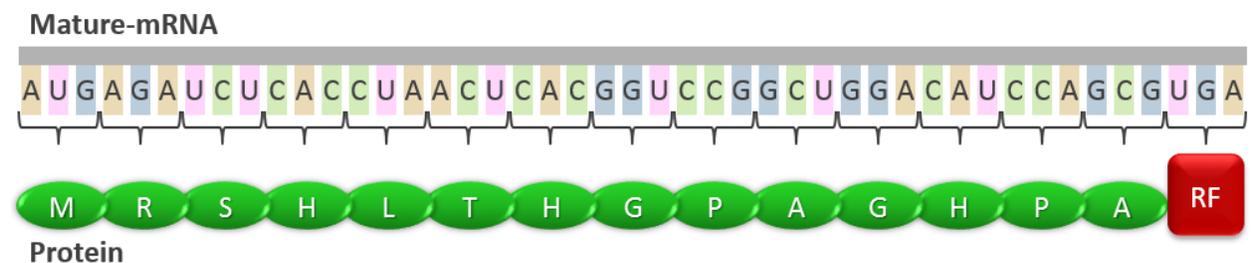
Figure A:



Translation

The ribosome translates mRNA into protein by reading the mRNA three nucleotides, or one codon, at a time. Each 3 nucleotide containing codon codes for a specific amino acid. Figure B, depicts a short mRNA sequence and its corresponding protein sequence.

Figure B:

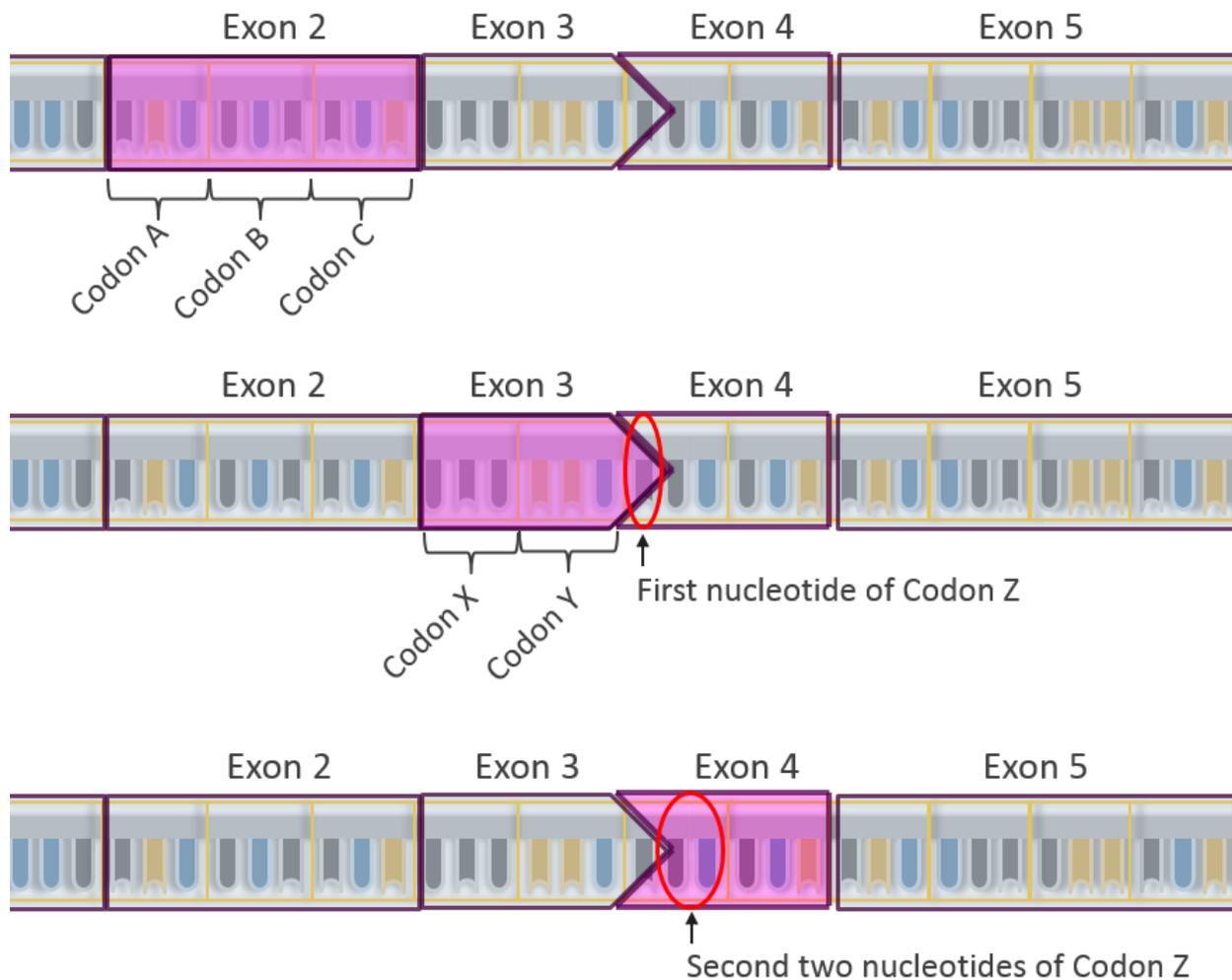


RF = release factor, binds to the stop codon to release the protein from the ribosome

Codon Splitting by Exons

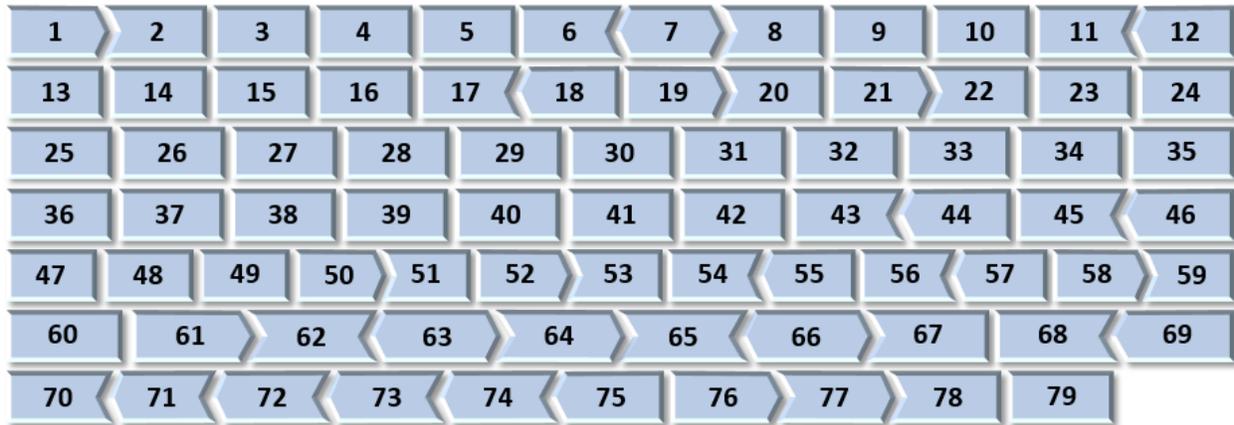
The codons of mRNA are not always evenly distributed between exons. The shape of the exon indicates the distribution of the codons. As shown in Figure C, the rectangular shaped exons contain whole codon units. In contrast, the arrow and chevron shaped exons split codons between them.

Figure C:



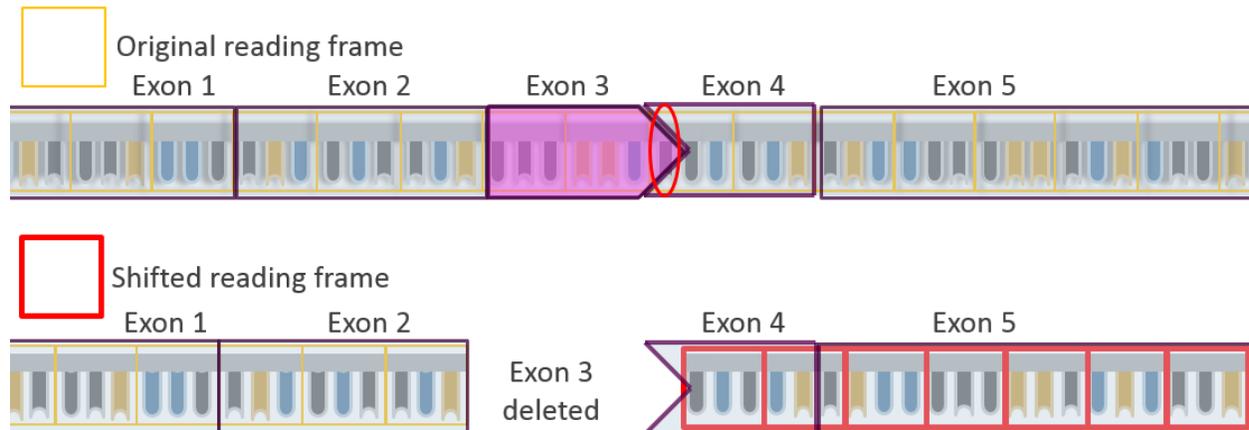
The dystrophin exon map is depicted in [Figure D](#). Dystrophin is the longest known human gene, containing 2.4 million base pairs and 79 exons. A number of exons in the dystrophin gene split codons between them.

Figure D:



If all the exons are present, the splitting of codons between exons has no effect on the final protein. However, if as shown in Figure E, an exon that splits a codon is missing due to genetic mutation, the mRNA reading frame following the mutation is shifted and all subsequent amino acids will be incorrect. The resulting protein is non-functional and unstable.

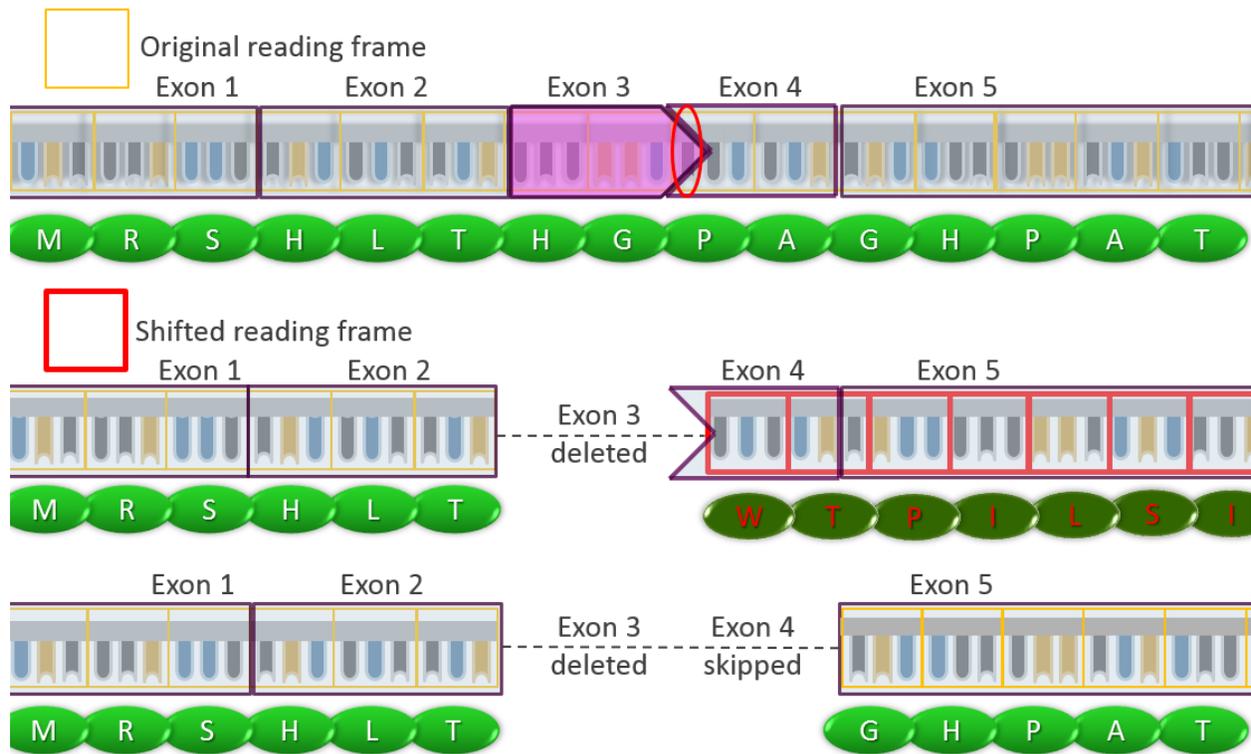
Figure E:



Restoration of the Reading Frame by Exon Skipping

Exon skipping aims to restore the mRNA reading frame by removing an additional exon from the final mRNA. As shown in Figure F, removal of an additional exon restores the reading frame following the mutation. The resulting protein will be missing the amino acids coded for by the missing exons, creating an internally deleted protein.

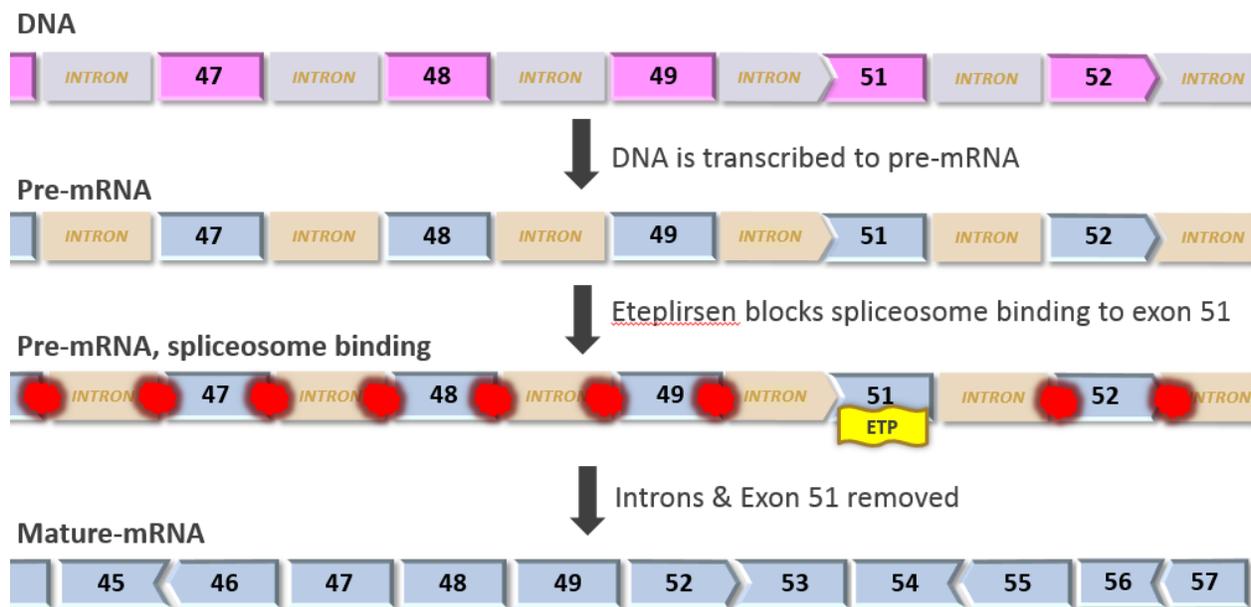
Figure F:



Eteplirsen Mechanism of Action

Eteplirsen enables exon skipping by binding to exon 51 of eteplirsen pre-mRNA and sterically hindering spliceosome binding. As shown in Figure G, if the spliceosome is unable to bind to exon 51, exon 51 will be removed along with the introns surrounding it and the reading frame will be restored.

Figure G:



Mutations Amenable to Exon 51 Skipping

A number of whole exon deletions are amenable to exon 51 skipping. Table A, provides examples that have been documented in the Leiden or UMD databases as well as the deletions tested in eteplirsen pivotal study 201/202.

Table A:

| Population | Whole Exon Deletions Amenable to Exon 51 Skipping |
|---|---|
| Deletion documented in the Leiden ¹ or UMD databases | 13-50, 19-50, 29-50, 31-50, 35-50, 40-50, 42-50, 45-50, 47-50, 48-50, 49-50, 50, 52 |
| Mutations tested in Eteplirsen study 201/202 | 45-50, 48-50, 49-50, 50, 52 |

¹ Leiden DMD Mutation Database [Internet]. Center for Human and Clinical Genetics – Leiden Medical Center. 2003 – [cited 2015 Dec 1]. Available from: <http://www.dmd.nl>

APPENDIX 19. SAREPTA CLARIFICATION OF STATEMENTS IN FDA BRIEFING DOCUMENT POSTED 15 JAN 2016

This appendix addresses Sarepta clarifications of statements in the FDA briefing document (posted 15 January 2016 and dated 22 January 2016)

Dystrophin Analytical Methodology:

| FDA Statement | Sarepta Clarification |
|---|---|
| <p><i>“It is important to note that the applicant digitally processed dystrophin images in their background material (images in Appendix 12) in such a way that low intensity values were preferentially increased to produce a higher intensity and higher contrast image.”</i></p> <p>(FDA BD page 29 of PDF)</p> | <p>The digitally processed images referenced by FDA in this statement were included in Sarepta’s briefing document for demonstration purposes only, and it is far more important to note that the referenced images were not used in the analysis of fiber intensity, nor to score dystrophin-positive fibers.</p> |
| <p><i>“Biomarker studies on the 4th biopsy obtained at Week 180 were conducted by the applicant with technical advice from FDA. However, the reliability of results remains questionable for a number of reasons, including the lack of independent confirmation.”</i></p> <p>(FDA BD page 30 of PDF)</p> | <p>Methodology for dystrophin analyses of the fourth biopsy tissue samples, including confirmatory assessments of percent dystrophin-positive fibers (PDPF) analysis performed by 3 independent pathologists, were agreed with FDA prior to conducting any analyses of the fourth biopsy tissue samples.</p> <p>In accordance with the mutually agreed-upon protocols for the assessment of dystrophin-positive fibers in DMD muscle biopsy samples from the fourth biopsy obtained at Week 180, 3 independent pathologists performed a blinded assessment of the randomized muscle fiber microscopy images, which independently confirmed the results obtained by the pathologist at Nationwide Children’s Hospital (NCH).</p> <p>Assessment of PDPF at NCH indicated a significant increase in PDPF score ($p<0.001$) relative to untreated control samples. This increase in PDPF score was confirmed by the 3 independent pathologists ($p<0.001$).</p> |

| FDA Statement | Sarepta Clarification |
|---|---|
| <p><i>“Random measurement error can be large in comparison to the estimated amount of dystrophin.”</i> (FDA BD page 31 of PDF)</p> | <p>The random measurement error of our Western blot protocol for measurement of dystrophin levels was well below the observed difference between untreated and treated Week 180 biopsy samples.</p> <p>A rigorous validation of the Western blot method was reviewed by the FDA prior to Week 180 biopsy analysis. Validation data demonstrated a %CV of +/- 50% and a linear range ($R^2 > 0.9$) of sensitivity extending as low as 0.25% of normal.</p> |
| <p><i>“There is no simple or reliable way to compare estimates of dystrophin amount derived from immunofluorescence with estimates derived from Western blot.”</i> (FDA BD page 35 PDF).</p> | <p>Correlation between dystrophin quantification by Western blot and IHC methods has been demonstrated by multiple laboratories (Taylor 2012; Anthony 2011; Anthony, 2014; Hathout 2015; FDA-NIH Workshop on Measuring Dystrophin 2015).</p> |
| <p><i>“In this context, the applicant selected three BMD patients as comparators for the Week 180 dystrophin studies, one of whom had low dystrophin level of about 2% of normal. However, the BMD patients selected by the applicant do not appear representative, and this patient may correspond to one of the rare BMD patients with very low dystrophin levels.”</i> (FDA BD page 34 of PDF)</p> | <p>BMD patient samples were not chosen to be representative; rather, they were selected in response to an FDA request to assess the relationship between dystrophin as measured by Western blot and immunofluorescence fiber intensity. Therefore, BMD samples were obtained that represented low, middle, and higher ranges of dystrophin expression. A comparable Western blot analysis-IHC correlation was presented by Hathout, et al. (MDA 2015 Scientific Conference poster; FDA-NIH Workshop on Measuring Dystrophin 2015), where BMD biopsies were chosen to represent low- and mid-level dystrophin expression. Consistently, their BMD low patient biopsy was 2% of normal.</p> |

Potential Clinical Impact:

| FDA Statement | Sarepta Clarification |
|---|--|
| <p><i>“With these two comparisons of eteplirsen to placebo, there was a positive finding for only the lower dose (30 mg/kg) and for just one of the two time points (the later time point). The lack of an effect with the higher dose group tends to undermine the finding in the lower dose group and the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point.”</i></p> <p>(FDA BD page 7 of PDF)</p> | <p>The study was designed to see whether dose (50 mg/kg vs. 30 mg/kg) or duration was the most important criterion to enable consistent dystrophin production.</p> <ul style="list-style-type: none"> • Duration of therapy was observed to be the critical variable when interpreting dystrophin levels. 12 weeks does not represent a clinically relevant duration of therapy (FDA BD page 26 of PDF). • Significant dystrophin levels were by measured at Week 24 for the 30 mg/kg dose, and, importantly, at Weeks 48 and 180 for both the 30 and 50 mg/kg doses by all dystrophin assay methods. |
| <p><i>“Arguably, placebo-treated patients who were blinded to treatment assignment from other controlled trials are more appropriate as matched controls than registry patients, as they may receive special care and attention as trial participants, and may be more highly motivated.”</i></p> <p>(FDA BD page 13 of PDF)</p> | <p>The placebo patients from another study as referenced by the FDA are not appropriate for comparison with the eteplirsen-treated patients (FDA BD pages 8, 9, 40-44, and 50 of the PDF):</p> <p>Baseline characteristics are not comparable between eteplirsen and the proposed placebo group:</p> <ul style="list-style-type: none"> • Placebo group included boys <7 years old • Placebo group included many patients with baseline 6MWT >440 meters which is outside the eteplirsen trial’s inclusion criteria <p>Placebo patients were followed for only one year, whereas eteplirsen-treated patients were followed for 3 or more years:</p> <ul style="list-style-type: none"> • By virtue of the ambulatory requirement at study entry, older placebo patients (e.g. ≥11 years) were a group of pre-selected, better performing subjects. • The first year of an 11-year-old-at-baseline placebo patient (i.e. 11-12 years old) to the third year of a 9-year-old boy with 3 years of eteplirsen treatment (i.e. 11-12 years old) is not a valid comparison due to the difference in duration of observation, as well as the biased selection of the 11-year -old ambulatory placebo boy, irrespective of both patients having the same age at last assessment. |

| FDA Statement | Sarepta Clarification |
|---|---|
| | <ul style="list-style-type: none"> • Comparison of eteplirsen-treated patients to the appropriately matched external control shows that more than one year is required to observe a divergence in disease progression between the two groups. |
| <p><i>“The robustness of the study result is a concern since a single patient could change the results substantially.”</i> (FDA BD page 69 of PDF)</p> | <p>This statement is inaccurate. A comprehensive sensitivity analysis was performed in order to address any potential issue regarding robustness of the data. Specifically:</p> <ul style="list-style-type: none"> • Two patients were removed: the best performing eteplirsen and the worst performing external control patient. • Results demonstrated a robust 6MWT treatment advantage of >100 meters with nominal significance. |
| <p><i>“Finally, as the sponsor’s natural history study proceeded, some patients left to enter interventional clinical trials, further decreasing the similarity of the natural history cohort to the eteplirsen patients.”</i> (FDA BD page 47 of PDF)</p> | <p>Two types of missing data sensitivity analyses were performed, the results confirmed that the magnitude of difference remained over 100 meters and nominal statistical significance was maintained:</p> <ul style="list-style-type: none"> • MMRM using all available data • Last Observation Carried Forward imputation (conservative analysis assuming that the 2 control patients did not decline) |
| <p><i>All patients in Study 202 have continued to progress steadily while taking eteplirsen, as indicated by rise time from floor, without any discernible stabilization or slowing. Most have now become unable, or nearly unable, to rise from the floor, which predicts a high likelihood of sequential loss of ambulation within 1 or 2 years.</i> (FDA BD page 24, to Fig 10)</p> | <p>Six patients lost the ability to rise without external support in the eteplirsen-treated group, including two boys with early loss of ambulation. For the four ambulant boys despite eventual loss of ability to rise from supine from Years 1 to 3 these eteplirsen patients did remain ambulant at Year 4.</p> |
| <p><i>Figure 2 shows the change over time in NSAA scores for all 12 eteplirsen-treated patients in Study 201/202. All show progressive declines in NSAA scores, with six patients moving to NSAA scores that have been reported to be associated with being within one year of loss of ambulation (ie., 9)</i> (FDA BD page 24-25)</p> | <p>Four patients had an NSAA score of 9 or less by Year 3 including two boys with early loss of ambulation. For the two ambulant boys despite eventual decrease of NSAA below 9 at Year 3 ambulation was preserved at Year 4.</p> |