CLINICAL STUDY PROTOCOL

DRUG:	Eteplirsen (Eteplirsen Injection)
STUDY NUMBER:	4658-204
STUDY TITLE:	An Open-Label, Multi-Center Study to Evaluate the Safety and Tolerability of Eteplirsen in Patients with Advanced Stage Duchenne Muscular Dystrophy
IND NUMBER:	CCI [redacted]
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	Amendment 1, 05 July 2016
PRIOR VERSION DATE:	Original, 30 June 2014

[redacted]

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	An Open-Label, Multi-Center Study to Evaluate the Safety and Tolerability of Eteplirsen in Patients with Advanced Stage Duchenne Muscular Dystrophy
Study No:	4658-204
Current Version Date:	Amendment 1 05 July 2016
Prior Version Date:	Original 30 June 2014

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product (IP).
- The ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and the European Clinical Trial Directive 2001/20/EC.

The Investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the IP.

PPD , MD Date

PPD

Sarepta Therapeutics Inc.
215 First Street
Cambridge, MA 02142 USA

INVESTIGATOR'S AGREEMENT

I have read Study No. 4658-204 Amendment 1 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Responsible Physician	PPD, MD, PhD	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 Telephone: PPD Mobile: PPD PPD

1. SYNOPSIS

NAME OF COMPANY Sarepta Therapeutics Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** Eteplirsen Injection **NAME OF ACTIVE INGREDIENT** Eteplirsen
TITLE: An Open-Label, Multicenter Study to Evaluate the Safety and Tolerability of Eteplirsen in Patients with Advanced Stage Duchenne Muscular Dystrophy	
Study Number: 4658-204	
Phase of Study: Phase 2	
INVESTIGATOR STUDY SITES: This study will be conducted at approximately 10 sites in the United States.	
OBJECTIVES: The primary objective of this study is to explore safety and tolerability of eteplirsen in patients with advanced stage Duchenne muscular dystrophy (DMD) patients who are amenable to exon 51 skipping. CCI [redacted] [redacted]	
METHODOLOGY: This is an open-label, multi-center study to explore the safety and tolerability of eteplirsen injection in patients with advanced stage DMD with confirmed genetic mutations amenable to treatment by exon 51 skipping. Patients will be evaluated for inclusion during a Screening/Baseline period of up to 4 weeks. Eligible patients will receive once weekly intravenous (IV) infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into a separate eteplirsen study. Safety will be regularly assessed throughout the study via the collection of adverse events (AEs), laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations. CCI [redacted]	
DURATION OF STUDY: Screening/Baseline Period: Up to approximately 4 weeks Treatment Period: 96 weeks Safety Extension Period: Up to 48 additional weeks until product is commercially available or until patients can transition into a separate eteplirsen study. Safety Follow-up Period: Four weeks following last infusion (as applicable) Total patient participation: Up to 148 weeks	
NUMBER OF PATIENTS: Approximately 20 patients will be enrolled in this study.	

NAME OF COMPANY	NAME OF FINISHED PRODUCT
Sarepta Therapeutics Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	Eteplirsen Injection **NAME OF ACTIVE INGREDIENT** Eteplirsen

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

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

1. Be a male with DMD with a mutation that may be amenable to exon 51 skipping (e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63) as documented by a genetic report from an accredited laboratory confirming mutation endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing.
2. Be between 7 and 21 years of age.
3. Has been on a stable dose of oral corticosteroids for at least 24 weeks prior to study drug administration and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study, or has not received corticosteroids for at least 24 weeks prior to study drug administration and does not expect to start corticosteroids throughout the study.
4. CCI [redacted]
5. Has a score of ≤4 on the Brooke Score for Arms and Shoulders.
6. Has cardiac and pulmonary function that, in the opinion of the investigator, is unlikely to decompensate over the study period.
7. Patients who are post-pubertal and sexually active must agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g., oral contraceptives).
8. Able to understand and comply with all study requirements, in the Investigator's opinion, or if under the age of 18 years, must have a parent(s) or legal guardian(s) who is able to understand and comply with all the study requirements.
9. Willing to provide informed consent to participate in the study, or if under the age of 18 years, be willing to provide informed assent, if applicable, and have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks of study drug administration that in the opinion of the Investigator might have an effect on muscle strength or function (e.g., growth hormone, anabolic steroids).
2. Previous treatment with SMT C1100/BMN 195 at any time.
3. Previous treatment with drisapersen (PRO051) within the last 6 months. Participation in any other DMD interventional clinical study within 12 weeks of study drug administration, or use of the shock training system or "STS," or planned use during this study. Concurrent participation in an interventional clinical study or observational trial is not permitted.
4. Major change in physiotherapy regimen within the past 3 months or expected change over the study period.
5. Major surgery within 3 months of study drug administration or planned major surgery for any time during this study.
6. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease or malignancy.

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7. Systemic use of any aminoglycoside antibiotic within 12 weeks of study drug administration or anticipated need for use of an aminoglycoside antibiotic or statin during the study.
8. CCI [redacted].
9. Must not require antiarrhythmic and/or antidiuretic therapy for heart failure. Patients are allowed to take other medication including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β blockers or potassium, provided they have been on a stable dose for 24 weeks prior to study drug administration and the dose is expected to remain constant throughout the study.
10. CCI [redacted].
11. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Eteplirsen 30 mg/kg will be administered as an IV infusion over approximately 35-60 minutes once a week for up to 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into a separate eteplirsen study.

REFERENCE TREATMENT:

None

CRITERIA FOR EVALUATION:

Safety Endpoints

The incidence of the following:

- Adverse events
- Clinical laboratory abnormalities
- Abnormalities in vital signs and physical examinations
- Abnormalities on ECGs and ECHOs

Exploratory Endpoints:

CCI [redacted]

NAME OF COMPANY	NAME OF FINISHED PRODUCT
Sarepta Therapeutics Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	Eteplirsen Injection **NAME OF ACTIVE INGREDIENT** Eteplirsen

CCI [redacted]

SAMPLE SIZE:

There is no formal sample size calculation. The sample size is based on qualitative considerations and is sufficient to provide safety evaluation of eteplirsen in the studied population.

STATISTICAL METHODS:

Safety Analyses

Treatment emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT). Non-emergent events will be recorded in the data listings. For all AE tables, the number and percentage of patients reporting AEs will be grouped by the Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT.

Descriptive statistics for ECG, ECHO, vital signs, and clinical laboratory parameters will be generated. Summary statistics for each parameter at the specific visits, as well as the change from Baseline to that visit, will also be displayed. All safety data will be presented in data listings.

CCI [redacted]

2. SCHEDULE OF EVENTS

Table 2: Treatment Period

Study Period	Screening	Treatment Period												
Week	**up to Week -4**	**BL/1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Informed Consent	X													
Inclusion/Exclusion	X	X												
Medical History	X													
Full Physical Exam	X	X	X		X			X						X
Brief Physical Exam				X		X	X				X			
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Lab Assessments	X	X[b]	X	X	X			X			X			X
CCI	■	■			■			■			■			■
CCI	■	■			■			■			■			■
Whole Blood (Genotyping/CCI)[c]	X													
Height and Ulnar Length	X	X			X			X			X			X
CCI	C													
CCI	■	■			■			■			■			■
■ CCI	■	■			■			■			■			■
■ CCI	■	■			■			■			■			■
CCI	■	■			■			■			■			■
ECG	X[f]				X			X			X			X
Holter ECG	X[f]													X
ECHO	X[f]				X			X			X			X
Study Drug Infusion		Once Weekly												
Conmed/Therapy	Continuous													
AE Assessment	Continuous													

Footnotes for Table 2 Schedule of Events: Screening through Week 48

Functional assessments, CCI , ECG, Holter ECG, and ECHO have a ±2 weeks window

[a] For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be collected only 30 minutes after the end of the infusion.

[b] Blood samples for the safety laboratory assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1. If more than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, it must be repeated. If less than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, additional safety laboratory assessments do not need to be performed.

[c] Patients may start dosing based on local genotyping results provided that these results fulfill the required inclusion criteria; however, all patients must undergo genetic testing to confirm the exon 51 skippable mutation and CCI .

[d] CCI

[e] CCI .

[f] Screening ECG, Holter ECG, and ECHO may be performed at any time during the Screening period; however results must be available on Day 1, prior to dosing.

[g] In the event of early termination prior to Week 96, the Week 96 assessments should be completed as the Early Termination Visit.

[h] End of Study visit should occur within 4 weeks after last dose

Study Period	Treatment Period												Safety Extension	End of Study[h]
Week	52	56	60	64	68	72	76	80	84	88	92	96/ET[g]	See Table 3	4 weeks after last infusion (as applicable)
Informed Consent														
Inclusion/Exclusion														
Medical History														
Full Physical Exam						X						X		X
Brief Physical Exam														
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X		X
Weight	X	X	X	X	X	X	X	X	X	X	X	X		X
Safety Lab Assessments[b]						X						X		X
CCI [redacted]						[redacted]						[redacted]		[redacted]
CCI [redacted]						[redacted]						[redacted]		
Whole Blood (Genotyping/CCI)[c]														
Height and Ulnar Length						X						X		
CCI [redacted]														
CCI [redacted]						[redacted]						[redacted]		
[redacted] CCI [redacted]						[redacted]						[redacted]		
[redacted] CCI [redacted]						[redacted]						[redacted]		
CCI [redacted]						[redacted]						[redacted]		
ECG						X						X		
Holter ECG												X		
ECHO						X						X		
Study Drug Infusion	Once Weekly													
Conmed/Therapy	Continuous													
AE Assessment	Continuous													

Footnotes for Table 2 Schedule of Events: Week 52 through End of Study

Functional assessments, CCI , ECG, Holter ECG, and ECHO have a ± 2 weeks window

[a] For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be collected only 30 minutes after the end of the infusion.

[b] Blood samples for the safety laboratory assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1. If more than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, it must be repeated. If less than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, additional safety laboratory assessments do not need to be performed.

[c] Patients may start dosing based on local genotyping results provided that these results fulfill the required inclusion criteria; however, all patients must undergo genetic testing to confirm the exon 51 skippable mutation and CCI .

[d] CCI

[e] CCI .

[f] Screening ECG, Holter ECG, and ECHO may be performed at any time during the Screening period; however results must be available on Day 1, prior to dosing.

[g] In the event of early termination prior to Week 96, the Week 96 assessments should be completed as the Early Termination visit.

[h] End of Study visit should occur within 4 weeks after last dose

Table 3: Safety Extension

Study Period	Safety Extension Period (Starting at Week 97 and continuing until the product is commercially available or until patients can transition into a separate eteplirsen study)	
Week	**120**	**144**
Full Physical Exam	X	X
Vital Signs[a]	Weekly	
Weight	Every 4 Weeks	
Safety Lab Assessments	X	X
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
ECG	X	X
ECHO	X	X
Study Drug Infusion	Once Weekly	
Conmed/Therapy	Continuous	
AE Assessment	Continuous	

Functional assessments, CCI, ECG, Holter ECG, and ECHO have a ±2 weeks window

[a] For infusion visits during the Safety Extension Period, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction in the past year of treatment, vital signs may be collected only 30 minutes after the end of the infusion.

3. TABLE OF CONTENTS AND LIST OF TABLES

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2D	2 dimensional
CCI [redacted]	[redacted]
ACE	angiotensin-converting enzyme
CCI [redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocking agent
AST	aspartate aminotransferase
BMD	Becker muscular dystrophy
BMI	body mass index
BUN	blood urea nitrogen
CD	compact disc
CFR	Code of Federal Regulations
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
ECG(s)	electrocardiogram(s)
ECHO(s)	echocardiogram(s)
EDC	electronic data capture
EF	ejection fraction
CC [redacted]	[redacted]
ET	early termination
CCI [redacted]	CCI [redacted]
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
HEENT	head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous, intravenously
KIM-1	kidney injury molecule-1
LDH	lactate dehydrogenase
CCI	[redacted]
LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities®
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
MPLA	multiplex ligation-dependent probe amplification
mRNA	messenger ribonucleic acid
NCS	Not clinically significant
CCI	[redacted]
PMO	phosphorodiamidate morpholino oligomer
PT	Preferred Term
CCI	[redacted]
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
CCI	[redacted]
STS	shock training system
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
US FDA	United States Food and Drug Administration
WBC	white blood cell

5. INTRODUCTION

5.1. Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare (estimated incidence of 1 in 3,500 to 5,000 live male births; CDC 2009; Emery 1991), degenerative, X-linked recessive genetic disorder caused by mutations in the dystrophin gene. In DMD, mutations in the dystrophin gene disrupt the open reading frame, resulting in an absence of functional 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, the stress of repeated muscle contraction causes cellular degeneration, regeneration, and inflammation, and, over time, myonecrosis.

The progression of DMD follows a highly predictable course. Significant motor deficits may be present during the first year of life, but diagnosis is usually made between the ages of 3 to 5 years when toddlers begin to show functional symptoms (e.g., waddling gait, toe walking, and difficulty climbing stairs). Over time, ambulation becomes increasingly abnormal, and by 8 years of age, most patients lose the ability to rise from the floor and climb stairs, and often fall while walking. By 10 to 14 years of age, most lose the ability to walk. Upper limb, cardiac, and diaphragmatic muscles progressively weaken during adolescence. Historically, patients died from respiratory or cardiac failure in their late teens or early 20s (Brooke 1989, Eagle 2002). Recent research suggests that use of ventilation support and steroids may increase life span by several years; however, DMD still has a mortality rate of 100% (Kohler 2009).

There are currently no disease-modifying treatments for DMD. Existing interventions are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation. Current pharmacologic treatments, such as corticosteroids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function (Beenakker 2005, Biggar 2006, Pradhan 2006). However, their benefits are only temporary, and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, Cushingoid facies and habitus, and cataracts (Biggar 2006, Manzur 2004).

5.2. Phosphorodiamidate Morpholino Oligomers (PMOs) for the Treatment of Duchenne Muscular Dystrophy

Phosphorodiamidate morpholino oligomers (PMOs) are a class of synthetic molecules based on a redesign of the natural nucleic acid structure. PMOs are distinguished from 2′-*O*-methyl and other antisense oligonucleotide platforms by the use of a six-membered morpholinyl ring which replaces the five-membered ribofuranosyl ring found in natural ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), and by the linkage of each morpholinyl ring through an uncharged phosphorodiamidate moiety (as opposed to negatively-charged phosphorothioate and other backbones used in most other RNA therapeutics). As a result of the combination of the morpholinyl rings and the uncharged linkages, PMOs have increased exon skipping activity and

have decreased nonspecific protein binding, with no detectable innate immune activation. The uniformity of the PMO backbone allows common synthetic, purification, formulation, and analytical methods to be used for all PMO drug candidates.

Approximately 80% of boys with DMD have mutations in the dystrophin gene that could be amenable to exon skipping therapies (Aartsma-Rus 2009). Thus, modulation of pre-messenger RNA (mRNA) splicing by exon skipping is a potentially useful treatment for DMD.

The active pharmaceutical ingredient of the investigational product (IP) eteplirsen injection is a CCI PMO that selectively binds to exon 51 of the dystrophin pre-mRNA. In doing so, it causes the exon to be skipped during processing and restores the mRNA open reading frame in patients with mutations amenable to skipping exon 51 of the dystrophin gene, which is approximately 13% of all DMD patients (Aartsma-Rus 2009). This is expected to enable the production of an internally deleted, yet partially functional, dystrophin protein, similar to that observed in Becker muscular dystrophy (BMD), a much less severe form of dystrophinopathy. In contrast to DMD, most BMD patients remain ambulatory and have a near-normal life expectancy (Bushby 1993).

5.3. Clinical Experience with Eteplirsen

Two Phase 1 clinical studies of eteplirsen have provided initial support and proof-of-concept for the safety and potential efficacy of eteplirsen in the treatment of DMD. In light of the positive findings from the two Phase 1 studies, a 28-week, double-blind, placebo-controlled Phase 2 study (Study 4658-us-201) was initiated to assess efficacy, safety, tolerability, and pharmacokinetics (PK) of eteplirsen. Twelve patients aged 7 to 13 years were randomized to receive once-weekly intravenous (IV) infusions of eteplirsen (30 or 50 mg/kg) for 28 weeks, or once-weekly placebo infusions for 24 weeks followed by eteplirsen infusion (30 or 50 mg/kg) for 4 weeks. At Week 28, these same 12 patients were enrolled in the extension study (Study 4658-us-202) where they continued open-label eteplirsen at the same dose they were receiving upon completion of the parent study. CCI [redacted] Two other eteplirsen studies are ongoing (Study 4658-203, a Phase 2 study in patients 4 to 6 years of age; and Study 4658-301, a Phase 3 confirmatory safety and efficacy study).

Based on the cumulative available safety data from these studies, eteplirsen has been shown to be well tolerated, with low rates of serious or severe adverse events (AEs). The following common AEs are categorized as adverse drug reactions given their frequency relative to placebo: headache, arthralgia, vomiting, nausea, upper respiratory tract infection, nasopharyngitis, and cough. In addition, the following events are also categorized as adverse drug reactions given their temporal relationship to eteplirsen administration: erythema, flushing, and mild temperature elevation.

[redacted].

5.4. Rationale for the Current Study

The purpose of this study is to evaluate the safety of eteplirsen in patients with advanced stage DMD with genetic mutations amenable to treatment by exon 51 skipping.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to explore safety and tolerability of eteplirsen in patients with advanced stage DMD who are amenable to exon 51 skipping.

6.2. Exploratory Objectives

CCI

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, multicenter study to explore the safety and tolerability of eteplirsen injection in approximately 20 patients with advanced stage DMD with confirmed genetic mutations amenable to treatment by exon 51 skipping.

Patients will be evaluated for inclusion during a Screening/Baseline period of up to 4 weeks. Written informed consent from the patient and/or parent/legal guardian and assent, if applicable, to participate in the study must be obtained prior to beginning any study-related procedures.

- Once eligibility is confirmed, patients will undergo Screening Assessments as indicated in Section 2 (Schedule of Events).
- Blood samples collected at the Screening Visit for the safety lab assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1.
  - However, if more than 2 weeks have elapsed since the collection of blood samples for the Screening safety lab assessments, it must be repeated.
  - If less than 2 weeks have elapsed since the collection of blood samples for the Screening safety lab assessments, additional safety lab assessments do not need to be performed, and the patient may proceed with Baseline/Week 1 assessments as indicated in Section 2.

Starting at Week 1, enrolled patients will receive once weekly IV infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into a separate eteplirsen study.

Safety will be regularly assessed throughout the study via the collection of AEs, laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations.

CCI [redacted]

Following the end of the weekly infusions, patients will be required to return to the study site for End of Study on-treatment safety evaluations.

The total duration including Screening, Treatment, Safety Extension, and End of Study Follow-up periods is approximately 148 weeks. The Safety Extension will start following completion of the Week 96 visit and is not to exceed 48 weeks. Dosing in the Safety Extension will continue until product is commercially available or until patients can transition into another study to receive eteplirsen.

Refer to Section 10 for the detailed list of study assessments.

7.2. Dose Selection Rationale

The dose of eteplirsen used in this study is 30 mg/kg. This dose was chosen based on results from the Phase 2, double-blind, placebo-controlled, multiple-dose study, Study 4658-us-201, and its open-label extension, Study 4658-us-202. As described in Section 5.3, these studies assessed the efficacy, safety, tolerability, and PK of 2 eteplirsen doses (50 and 30 mg/kg) administered as IV infusions in twelve 7- to 13-year-old pediatric patients diagnosed with DMD with out of frame mutations amenable to treatment by skipping exon 51.

Once weekly treatment with 30 mg/kg eteplirsen for 24 weeks significantly increased the mean percentage of dystrophin-positive muscle fibers as percent (%) of normal in DMD patients compared to placebo.

At Week 48, increases in the percent of dystrophin-positive fibers were similar for patients who had received weekly 30 and 50 mg/kg eteplirsen without interruption from Week 1 (52% and 42% of normal, respectively or 47% for the combined groups). These data suggest that the effect of eteplirsen on the production of novel dystrophin is not significantly different between the two doses tested in this study. Therefore, the lower dose was selected as the more conservative choice, because patients presumably would receive this drug as a life-long treatment.

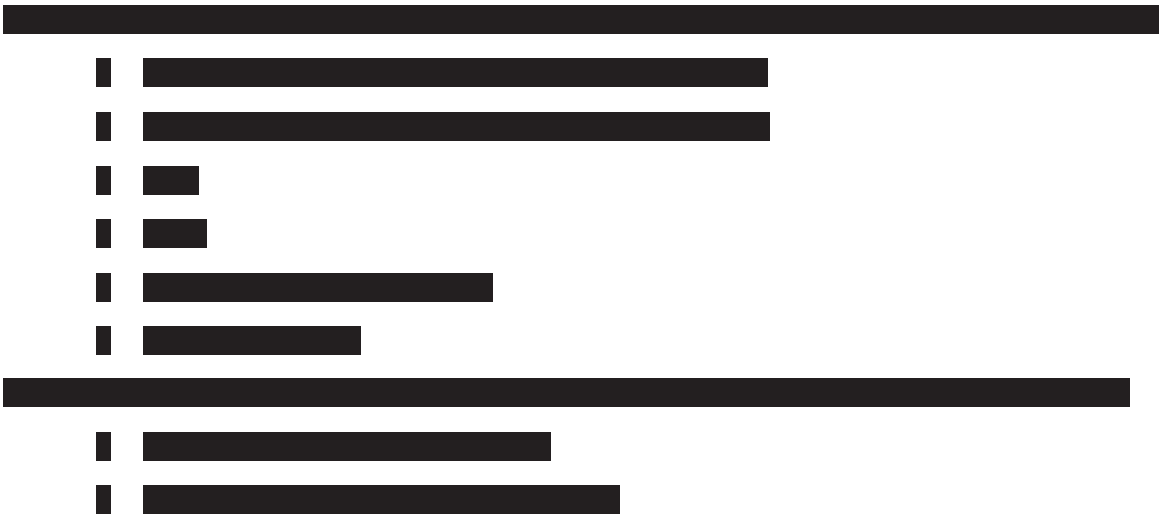
7.3. Study Endpoints

7.3.1. Safety Endpoints

Incidence of:

- Adverse events
- Clinical laboratory abnormalities
- Abnormalities in vital signs and physical examinations
- Abnormalities on electrocardiograms (ECGs) and echocardiograms (ECHO)

7.3.2. CCI



7.4. Discussion of Study Design

This is an open-label study to provide safety data in patients with advanced stage DMD. The study focuses on safety assessments; however, because a majority of patients with advanced stage DMD are non-ambulatory, CCI

The 96-week duration of the study provides sufficient follow-up time to obtain safety data in this population. The safety extension (not to exceed 48 weeks) will allow patients who have been receiving once weekly infusions of eteplirsen in Study 4658-204 to continue treatment until the product is commercially available or they are able to transition to another eteplirsen study.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Number of Patients

Approximately 20 patients will be enrolled in this study.

8.2. Patient Inclusion Criteria

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

1. Be a male with DMD with a mutation that may be amenable to exon 51 skipping (e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63) as documented by a genetic report from an accredited laboratory confirming mutation endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing.
2. Be between 7 and 21 years of age.
3. Has been on a stable dose of oral corticosteroids for at least 24 weeks prior to study drug administration and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study, or has not received corticosteroids for at least 24 weeks prior to study drug administration and does not expect to start corticosteroids throughout the study.
4. CCI [redacted]
5. Has a score of ≤4 on the Brooke Score for Arms and Shoulders.
6. Has cardiac and pulmonary function that, in the opinion of the investigator, is unlikely to decompensate over the study period.
7. Patients who are post-pubertal and sexually active must agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g., oral contraceptives).
8. Able to understand and comply with all study requirements, in the Investigator's opinion, or if under the age of 18 years, must have a parent(s) or legal guardian(s) who is able to understand and comply with all the study requirements.
9. Willing to provide informed consent to participate in the study, or if under the age of 18 years, be willing to provide informed assent, if applicable, 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.

8.3. Patient Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks of study drug administration that in the opinion of the Investigator might have an effect on muscle strength or function (e.g., growth hormone, anabolic steroids).
2. Previous treatment with SMT C1100/BMN 195 at any time.
3. Previous treatment with drisapersen (PRO051) within the last 6 months. Participation in any other DMD interventional clinical study within 12 weeks of study drug administration, or use of the shock training system or "STS," or planned use during this study. Concurrent participation in an interventional clinical study or observational trial is not permitted.
4. Major change in physiotherapy regimen within the past 3 months or expected change over the study period.
5. Major surgery within 3 months of study drug administration or planned major surgery for any time during this study.
6. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease or malignancy.
7. Systemic use of any aminoglycoside antibiotic within 12 weeks of study drug administration or anticipated need for use of an aminoglycoside antibiotic or statin during the study.
8. CCI [redacted].
9. Must not require antiarrhythmic and/or antidiuretic therapy for heart failure. Patients are allowed to take other medication including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β blockers or potassium, provided they have been on a stable dose for 24 weeks prior to study drug administration and the dose is expected to remain constant throughout the study.
10. CCI [redacted].
11. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results.

8.4. Completion of a Patient's Participation in the Study

The length of a patient's participation may be from the time the informed consent form is signed up to Week 148 or up until the product is commercially available or until the patient transitions into a separate eteplirsen study.

8.5. Patient Withdrawal Criteria

Any patient can decide to withdraw from study participation at any time for any reason. In addition, the study Sponsor may decide to stop the study participation of any patient as deemed necessary. The Investigator may also stop the study participation of any patient at any time. Reasons for study withdrawal include but are not limited to:

- The patient was erroneously included in the study (i.e., was found to have not met the eligibility criteria).
- The patient experiences an intolerable or unacceptable AE.
- The patient is unable to comply with the requirements of the protocol.
- The patient participates in another investigational study without the prior written authorization of the Sponsor.

The Investigator or study staff will document the reason(s) for treatment discontinuation on the case report form (CRF).

Patients who received at least 1 dose of IP who discontinue from treatment within 4 weeks after a functional assessment visit will be asked to return for an End of Study visit within 4 weeks of their last visit. Patients who received at least one (1) dose of IP who discontinue treatment more than 4 weeks after a functional assessment visit will be asked to complete all Early Termination (Week 96) assessments within 30 days of discontinuation and a subsequent End of Study visit within 4 weeks of the Early Termination (ET) visit.

Following Week 96, patients may continue to receive eteplirsen for up to an additional 48 weeks and be followed as described in the Safety Extension portion of Section 2, Table 3 (Safety Extension Schedule of Events). They may receive weekly infusions of eteplirsen at the same dose, with continuous monitoring of adverse events and concomitant medications, while undergoing physical examination and safety laboratory assessments every 24 weeks. If patients discontinue eteplirsen during the Safety Extension, they will be asked to return for an End of Study visit 4 weeks after their final dose.

Patients who discontinue eteplirsen dosing in the Safety Extension Period in order to transition onto commercial drug or into a separate eteplirsen study do not require an End of Study visit.

8.6. Study Discontinuation

If the Sponsor, the Investigator, the medical monitor, the study monitor, institutional review board/independent ethics committee(s) (IRB/IEC), or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among (at a minimum) the Sponsor, the Investigator, IRB/IEC and the medical monitor.

Conditions that may warrant termination of the study or an individual site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements consistent with 21 CFR 312 or the European Clinical Trial Directive 2001/20/EC

Study termination and follow-up will be performed in compliance with the conditions set forth in International Conference on Harmonisation (ICH) E6 on Good Clinical Practice (GCP) as well as 21 CFR 312.56b and the European Clinical Trial Directive 2001/20/EC which require a Sponsor to ensure an Investigator's compliance with these requirements and to promptly secure a plan for compliance or discontinue shipments of the IP to the Investigator and end the Investigator's participation in the study.

9. TREATMENT OF PATIENTS

9.1. Investigational Product

Eteplirsen Injection

9.1.1. Packaging and Labeling

Please refer to the study-specific Pharmacy Manual for information on packaging and labeling.

The label text for the IP will at a minimum include the following information: product name/identifier, cautionary statement per 21 CFR 312.6, lot number (or alternative code), storage conditions, and the name of the Sponsor.

9.1.2. Storage

Vials of IP must be stored in a secured, limited-access area with appropriate temperature recording, controls, and monitoring. Details for IP handling, storage and for preparation of the diluted IP for administration can be found in the study specific Pharmacy Manual.

9.2. Treatments Administered

Eligible patients will receive a weekly IV infusion of 30-mg/kg dose of eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into a separate eteplirsen study.

The dose of eteplirsen will be calculated based on the most recent patient weight obtained at the site prior to the current visit. Eteplirsen should be prepared for dosing by following the steps detailed in the study-specific Pharmacy Manual.

Eteplirsen will be administered as an IV infusion over a period of approximately 35 to 60 minutes, or approximately 5 mL/min. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5%, or LMX4 cream) be applied to the infusion site prior to each administration of eteplirsen. Additional administration and IP details are available in the study-specific Pharmacy Manual.

An implanted venous access port may be inserted for eteplirsen administration at the discretion of the Investigator. If eteplirsen is administered into an existing IV line, the line should be flushed with normal saline before and after administration of eteplirsen. After eteplirsen administration and the saline flush, the port may be flushed with heparin to heplock the port prior to removal of the infusion line.

No other medications may be administered concomitantly during the eteplirsen infusion.

All treated patients will be observed for at least 1 hour following the end of each eteplirsen infusion.

In-home study treatment administration by a visiting nurse may be available after Week 48.

The following guidelines for the timing of dosing should be followed throughout the study:

1. Patients should receive eteplirsen once every 7 days starting on Study Day 1. A window of ±3 days from the scheduled dose is acceptable after the first infusion.
2. Patients may not receive 2 separate doses of eteplirsen within the same 60-hour period.
3. The medical monitor should be contacted in the event of ≥2 consecutive missed doses.

9.2.1. Dose Modification, Reduction, or Delay

There is no provision for dose alteration in this study. If a patient experiences an AE that requires interruption of administration of eteplirsen for ≥2 consecutive doses, the Investigator will consult with the Medical Monitor to determine whether the patient may resume treatment.

9.3. Randomization and Blinding

This is an open-label study, and therefore all patients will receive eteplirsen.

9.4. Prior and Concomitant Medications

The dosing regimen for oral corticosteroids for treatment of DMD including, but not limited to, prednisolone and prednisone, should be kept the same throughout the study.

The following therapies may be used before enrollment and throughout the study; however, the dosage should be constant throughout the treatment period, unless clinically indicated:

- Oral ACE inhibitors, including but not limited to perindopril and lisinopril
- Oral β-blockers, including but not limited to carvedilol and atenolol
- Angiotensin-receptor blockers, including but not limited to losartan, irbesartan, valsartan, and candesartan
- Oral laxatives, including but not limited to lactulose, Senokot, and Movicol
- Vitamin D and calcium supplements
- Alendronate (Fosamax) or other bisphosphonates used to treat osteoporosis/osteopenia by inhibiting osteoclasts
- Over-the-counter herbal preparations, including herbal supplements, vitamins, minerals, and homeopathic preparations, provided the patient had been on stable doses for 24 weeks before enrollment in this study

Other concomitant medications (e.g., vitamins or other non-RNA antisense medications) may also be taken if, in the opinion of the Investigator, they do not interfere with study assessments and outcomes. The Investigator should contact the Medical Monitor if he/she is unsure of the impact of a concomitant medication on study assessments and outcomes. Every attempt should be made to keep the dosage constant throughout the study period (i.e., through Week 96); although modifications to accommodate changes in weight are permitted.

Introduction of new physiotherapy interventions during the course of the study must be avoided unless the best interests of the patient are at risk. Should a contracture develop during the course

of the study, and it is considered in the best interest of the patient to treat the contracture, then any of the following interventions may be used to reduce the contracture, but they must be clearly documented:

- Contracture control devices
- Night splints
- Stretching exercises (passive, active, self)
- Serial casting

The following therapies are **not permitted** during the conduct of this study:

- Systemic or oral steroids for non-DMD conditions
- Investigational agents for the treatment of DMD
- Any medication with the potential to affect muscle mass, strength, and/or function, such as, but not limited to, growth hormone and PDE-5 inhibitors
- Immunosuppressants (other than oral or systemic corticosteroids, as outlined)
- Systemic aminoglycoside antibiotics (unless discussed and agreed upon with the Investigator and the Medical Monitor)
- Statins (unless discussed and agreed upon with the Investigator and Medical Monitor)

9.5. Treatment Compliance

Treatment compliance will be assessed via compliance with scheduled weekly infusions.

10. STUDY ASSESSMENTS

10.1. Study Schedule of Events

A detailed schedule of the study assessments and times is shown in Section 2.

10.2. Assessments at the Screening/Baseline Visits

10.2.1. Informed Consent

Written informed consent from the patient or parent/legal guardian(s) and assent from the patient (if applicable) to participate in this study must be obtained prior to beginning any of the procedures for this study.

10.2.2. Medical History

Medical history will be obtained for all patients.

10.2.3. Blood samples for DMD Genotyping and [redacted]

Blood samples will be obtained at Screening for confirmation of DMD genotyping. Patients may start dosing based on local genotyping results provided that these results fulfill the required criteria described in Section 8.2; however, all patients must undergo genetic testing to confirm the exon 51 skippable mutation. Patients whose genotype is not confirmed to be exon 51 skippable will be excluded from continuing in this trial. [redacted]

10.3. Safety Assessments

10.3.1. Physical Examination

Physical examinations, full and brief, will be conducted at the time points specified in Section 2. Physical examinations will be performed by the Investigator, a physician Sub-Investigator, or a Nurse Practitioner (if licensed in the state or province to perform physical examinations). Full physical examinations will include examination of general appearance; head, ears, eyes nose, and throat (HEENT); heart; lungs; chest; abdomen; skin; lymph nodes; musculoskeletal; and neurological systems. Brief physical examinations will include examination of general appearance, HEENT, heart, lungs, chest, abdomen, and skin.

10.3.2. Vital Signs and Weight

Vital signs (blood pressure, heart rate, respiration, and oral temperature) and weight will be measured at the time points specified in Section 2.

For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be collected only 30 minutes after the end of the infusion. All assessments will be performed after patients have remained seated for 5 minutes. Pulse rate and respiratory rate should be measured over 1 minute.

Details about how weight measurements are obtained are provided in the Clinical Evaluator Manual. If a patient's weight varies by more than 10% from the prior visit, the patient should be re-weighed to confirm the result, and an explanation of the change should be documented.

10.3.3. Clinical Laboratory Evaluations

The following routine clinical laboratory tests will be collected at the time points specified in Section 2 and analyzed by an accredited central laboratory selected by the Sponsor and prepared according to the Laboratory Manual provided for the study:

Chemistry:	Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactase dehydrogenase (LDH), C-reactive protein (CRP), creatine kinase (CK), and serum cystatin C
Hematology:	Red blood cells (RBCs), total white blood cells (WBCs), hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells
Coagulation Screen:	Prothrombin time, International Normalized Ratio (INR), and activated partial thromboplastin time (aPTT)
Urinalysis:	pH, specific gravity, protein, glucose, ketones, cytology, hemoglobin, and kidney injury molecule-1 (KIM-1)

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will determine whether abnormal assessment results are clinically significant (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in assessment results that has medical relevance resulting in an alteration in medical care. If clinically significant deterioration from baseline levels is noted, the Investigator will continue to monitor the patient with additional assessments until:

- Values have reached normal range and/or baseline levels; or
- In the judgment of the Investigator together with the Sponsor's Medical Monitor, abnormal values assessed to be not related to the administration of investigational

product or other protocol-specific procedures, and additional assessments are not medically indicated.

10.3.4. Height and Ulnar Length

Height and ulnar length will be measured at the time points specified in Section 2.

Height should be measured with shoes off. If standing height cannot be obtained, height should be calculated using the following equation (Gauld 2004):

$$\text{Height (cm)} = 4.605U + 1.308A + 28.003$$

where U is length of the ulna measured using an anthropometer or callipers, and A is patient's age (years).

10.3.5. Electrocardiogram

Twelve-lead ECGs and Holter ECGs will be obtained at the time points specified in Section 2. ECGs will be performed at a consistent time of day throughout the study. ECGs will be performed only after the patient is in the supine position, resting, and quiet for a minimum of 15 minutes. The ECG will be manually reviewed and interpreted by medically qualified personnel using a central vendor according to pre-specified criteria. The Investigator will review the results of the centrally read ECG report and determine if the findings are clinically significant.

10.3.6. Echocardiogram

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in Section 2. ECHOs will be performed at a consistent time of day throughout the study. The ECHO will be reviewed and interpreted by medically qualified personnel using a central vendor according to pre-specified criteria. Ejection fraction (EF) will be noted. The Investigator will review the results of the ECHO report and determine if the findings are clinically significant.

10.3.7. Concomitant Medications and Therapies

Concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be reviewed and recorded at each visit from the time the patient signs informed consent, or parent/legal guardian signs informed consent and the patient signs the assent form (if applicable). Information on any physiotherapeutic intervention must be collected in detail for this study.

10.3.8. Adverse Events

The collection of adverse events is described in Section 11.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

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CCI [redacted]

[redacted].

CCI [redacted]

CCI [redacted]

CCI [redacted]

11. ADVERSE EVENTS

11.1. Collection of Adverse Events

Over the entire duration of the study, site personnel will ensure that all AEs are recorded appropriately. If an AE occurs, the primary concern is for patient safety, and the Investigator will use their judgment and expertise to determine the appropriate course of action.

All AEs from the time of informed consent through study completion or study discontinuation will be recorded in each individual patient's CRF. For patients who prematurely discontinue the study (see Section 8.5), AEs will continue to be recorded until 4 weeks after the last eteplirsen infusion.

If, at any time after the patient has completed participation in the study (see Section 8.5), the Investigator or study staff becomes aware of a serious adverse event (SAE) that the Investigator believes is possibly/probably or definitely related to the IP (Section 11.3.1) or is possibly/probably or definitely related to a study procedure (Section 11.3.2), then the event and any known details must be reported promptly to the Sponsor.

11.2. Definition of Adverse Events

11.2.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with the investigational drug. An AE can, therefore, be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality that occurs during or after administration of an IP whether or not considered related to the IP. Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or worsen during the AE collection period.

11.2.2. Serious Adverse Event (SAE)

An SAE is defined as any AE that results in any of the following:

- **Death**: The patient died as the result of the event.
- **Life-threatening event**: Any AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.

- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations.
- **Persistent or significant disability/incapacity**: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the IP.
- **Important medical events**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.3. Classification of Adverse Events

Each AE whether serious or nonserious will be classified by the Investigator according to the following rules and definitions.

11.3.1. Relationship to Investigational Product

For each AE, the Investigator determines whether there is a reasonable likelihood that the AE may have been caused by the study treatment according to the categories below:

Unrelated: The event is clearly not related to the IP

Possibly/probably related: The event could be related/is likely to be related to the IP

Definitely related: The event is clearly related to the IP

AEs that the Investigator or Sponsor considers to be possibly, probably, or definitely related to the IP will be considered adverse drug reactions.

11.3.2. Relationship to Study Procedures

For each AE the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study procedures according to the categories below:

Unrelated: The event is clearly not related to the study procedures

Possibly/probably related: The event could be related/is likely to be related to study procedures

Definitely related: The event is clearly related to the study procedures

11.3.3. Relationship to Underlying Disease

For each AE the Investigator determines whether there is a reasonable possibility that the AE may be related to the underlying disease according to the categories below:

Unrelated:	The event is clearly not related to the underlying disease
Possibly/probably related:	The event could be related/is likely to be related to the underlying disease
Definitely related:	The event is clearly related to the underlying disease

Events of disease progression may be considered AEs, based on the investigator's discretion.

11.3.4. Severity of Adverse Events

Note that severity is not the same as "seriousness," which is defined in Section 11.2.2 and which serves as a guide for defining regulatory reporting obligations.

The Investigator will assess the severity of all AEs as Mild, Moderate, or Severe, based on the following definitions:

Mild:	The event does not interfere with the patient's usual activities.
Moderate:	The event interferes with the patient's usual activities.
Severe:	The event prevents the patient from undertaking their usual activities and requires therapeutic intervention or cessation of the IP.

11.3.5. Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the patient outcome of each AE.

11.3.6. Action Taken Regarding the Investigational Drug Product

The Investigator will provide information regarding the action taken with respect to the IP in response to the AE.

11.3.7. Expectedness of an Adverse Event

The expectedness of all AEs will be determined according to the most recent version of the Investigator's Brochure for eteplirsen.

11.3.8. Suspected Unexpected Serious Adverse Reactions (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) will be handled by appropriate personnel at the Sponsor or designee and reported within the required timelines in an unblinded fashion to regulatory authorities and IRB/IEC per the requirements of the concerned competent bodies. SUSARs will also be reported to study Investigators.

11.4. Recording Adverse Events

All AEs/SAEs experienced from the time of informed consent/assent to the last follow-up will be recorded within each patient's CRF. Information should include: a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to IP or study procedure or underlying disease; and any action taken will be recorded. Resolution occurs when the patient has returned to his baseline state of health or further improvement or worsening of the event is not expected.

Whenever possible, a diagnosis will be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. Several symptoms or laboratory results that are related to the same diagnosis can thus be part of the same AE. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE. All AEs will be followed until the resolution of AE, completion of the patient's study participation, or study termination, whichever occurs first. SAEs will be followed until resolution or until the condition stabilizes or returns to baseline status.

11.5. Reporting Serious Adverse Events

It is the responsibility of the Investigator that reporting is done adequately. In order to meet Regulatory reporting timelines, the study site is obligated to report any SAE(s) to the Sponsor or designee immediately and no later than 24 hours after receiving information of an event that meets at least one of the criteria for seriousness as defined in Section 11.2.2. Refer to the SAE Reporting Plan for further details on the submission of SAE Reports.

11.6. Special Situations

11.6.1. Overdose

An overdose is defined as administration of a dose that is over 50 mg/kg. An overdose is not an AE. An overdose will be reported even if it does not result in an AE. An overdose will be recorded in the source documents and reported to the Sponsor or designee within 24 hours.

11.6.2. Death

Death is an outcome of an event. All causes of death are SAEs. In the event of death, every effort should be made to obtain a death certificate and if possible, an autopsy report. If the cause of death is unknown, death will be recorded as the event.

11.6.3. Responsibilities of the Investigator

The responsibilities of the Investigator include but are not limited to the following:

- Monitor and record all AEs
- Determine seriousness, severity, and relationship to IP and/or study procedure and/or underlying disease

- Determination of the onset and end date of each event
- Provide initial report on all SAEs within 24 hours of knowledge to the Sponsor or designee
- Provide follow-up information on SAEs in a timely and proactive manner
- Respond to queries regarding AEs and SAEs in a timely manner
- Ensure source documentation for all AEs are accurate and complete
- Ensure that the study is conducted as defined in this document

11.6.4. Responsibilities of the Sponsor

The responsibilities of the study Sponsor (Sarepta Therapeutics, Inc.) include but are not limited to the following:

- Training of Investigator and site staff on AE/SAE definitions, safety assessments, and site obligations related to safety monitoring and reporting of AE/SAEs
- Training with regard to the accurate and legal reporting of SAEs to all applicable regulatory bodies, IRBs/IECs, clinical trial sites, and other parties as appropriate and required within the regulated timing
- Recording of AEs
- Notification of expedited SAEs to sites
- Annual safety reporting to regulatory authorities and IRBs/IECs according to regional requirements

12. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

12.1. Recording of Data

Clinical data for this study will be captured in an electronic format. Electronic data capture (EDC) will be provided by a contract research organization. The Investigator, or personnel delegated by the Investigator, will perform primary data collection/perform assessments based on the protocol design and captured in source documentation. All required study information must be recorded on the appropriate CRF screens/forms using the CRF Completion Guidelines for the study. A CRF must be completed for each patient that is enrolled. The study monitor will conduct 100% source data verification to ensure maximum data integrity. All data must be carefully entered in a timely fashion to permit meaningful interpretation and study oversight.

12.2. Quality Assurance

The CRFs will be reviewed at regular intervals by a clinical monitor from the Sponsor or a representative of the Sponsor per the agreed upon Monitoring Plan against the source documentation for identification and clarification of any discrepancies. Automated and manual quality checks will be in place to identify discrepancies, such as missing data, protocol deviations, out-of-range data, other data inconsistencies and compliance. Requests for data clarification or correction will be documented as electronic queries within the CRF and for the Investigator or study coordinator to resolve. All changes to the CRFs will be tracked in an electronic audit trail. Site Study Files will be reviewed for compliance throughout the study.

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by IRBs/IECs or regulatory authorities before, during, or after the study. The Investigator will allow and assist the Sponsor's representatives and any regulatory agency to have direct access to all study records, CRFs, patient medical records and other source documentation, IP dispensing records and IP storage area, study facilities, and any other source documentation.

The Investigator must make study files and data accessible to the study monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors such as the United States Food and Drug Administration (US FDA).

12.3. Retention of Study Documents

At study completion, all CRF data for an individual site will be copied onto a compact disc (CD) and provided to the Investigator for retention in the Study Files. The supporting Site Study Files must be retained by the Investigator for a period of 3 years after the investigation is discontinued and regulatory authorities are notified.

However, these documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the

Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed upon designee.

Patient records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

13. STATISTICS

13.1. General Considerations

This section describes the rules, conventions, statistical analysis, and presentation of data for this study. Full details will be provided in the Statistical Analysis Plan (SAP) for this study.

Revisions during the study may be made to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. Any revisions will be based on blinded review of the data. A formal SAP for the analysis and presentation of data from this study will be prepared and issued before database lock. The SAP will provide a more technical and detailed description of the proposed data analysis methods and procedures. Deviations from the statistical analyses outlined in this protocol will be included in this plan; any further modifications will be noted in the clinical study report (CSR). All statistical analyses will be performed by or under supervision of the Sponsor.

All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Percentages of patients with AEs or laboratory abnormalities will be based on nonmissing values.

All data collected in this study will be presented using summary tables and patient data listings. Summary statistics for raw and change from Baseline data of continuous variables will minimally include n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Endpoints will be assessed primarily using simple descriptive statistics and/or inferential statistics. Baseline will generally be defined as the last available value before dosing.

13.2. Determination of Sample Size

There is no formal sample size calculation. The sample size is based on qualitative considerations and is sufficient to provide safety evaluation of eteplirsen in the studied population.

13.3. Analysis Sets

There will be one analysis population, the Safety set, which includes all patients who are enrolled in the study and receive at least 1 dose of eteplirsen.

13.4. Protocol Deviations

A listing of protocol deviations will be provided. This deviation listing will be based on the review of study data prior to locking the database and will include the nature of the deviation (e.g., inclusion/exclusion, prohibited therapies).

13.5. Disposition, Demographics, and Baseline Characteristics

The number and percentage of patients completing or prematurely discontinuing the study will be summarized. Reasons for premature discontinuation will also be summarized.

Demographic characteristics including age (years), race, ethnicity, and baseline characteristics including height (cm), weight (kg), body mass index (BMI; kg/m^2), CCI [redacted] will be summarized. Demographic data and baseline characteristics will be presented in data listings.

13.6. Medical History

Medical history will be presented in data listings.

13.7. Dosing and Compliance

The cumulative exposure to eteplirsen, total volume of drug administered (mL), total number of infusions received, and the cumulative amount of drug received will be summarized by dose group for all treated patients. Dosing information will be provided in a data listing.

13.8. Safety Analysis

13.8.1. Safety Variables

Incidence of:

- AEs
- Clinical laboratory abnormalities
- Abnormalities in vital signs and physical examinations
- Abnormalities on ECGs and ECHO

13.8.2. Safety Analyses

Safety analyses will be descriptive in nature. Summary statistics for each parameter at a specific visit, as well as the change from Baseline to that visit, will also be displayed. All safety data will be presented in the data listings.

13.8.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be summarized. Non-emergent events will be recorded in data listings. For all AE tables, the number and percent of patients reporting AEs (grouped by the Medical Dictionary for Regulatory Activities [MedDRA] System Organ Class [SOC] and Preferred Term [PT]) will be summarized by treatment condition. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

Multiple occurrences of the same AE (at the PT level) in the same patient will be counted only once in frequency tables. If a patient experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship and maximum severity to

IP will be used to summarize AEs by relationship and severity. Treatment-related TEAEs will be defined as those that the Investigator considers possibly/probably or definitely related to the IP.

The following summary tables will be produced:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- SAEs

In addition, all SAEs, regardless of their treatment-emergent status will be summarized by SOC and PT.

The following listings will be produced:

- Non-treatment emergent AEs
- All TEAEs
- AEs leading to discontinuation
- SAEs

13.8.2.2. Physical Examination, Vital Signs, Weight, and Height/Ulnar Length

Vital signs, weight, and height/ulnar length will be presented by treatment condition and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics. Frequency tables of predefined change abnormal in vital sign values will be generated.

Results from physical examinations will be presented in patient data listings.

13.8.2.3. Clinical Laboratory Tests

Clinical chemistry, hematology, coagulation, and urinalysis will be presented by treatment condition and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics for each continuous, and frequency tables for each discrete parameter. Frequency tables of predefined change abnormal of select laboratory parameter values will be generated.

13.8.2.4. Electrocardiograms and Holter Electrocardiograms

The actual value and change from Baseline to each visit will be presented by treatment condition and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics. Shift and frequency tables of predefined change abnormal of select ECG parameter values will be generated.

13.8.2.5. Echocardiograms

The actual value and change from Baseline to each visit will be summarized by treatment condition for each ECHO for EF.

13.8.2.6. Prior and Concomitant Medications and Physiotherapeutic Interventions

All prior and concomitant medications, as well as physiotherapeutic interventions, will be presented in data listings.

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13.10. Interim Analysis

No interim analysis is planned for this study.

13.11. Other Statistical Issues

Additional analyses may be conducted. Any such analyses will be detailed in the SAP.

14. SPECIAL REQUIREMENTS AND PROCEDURES

14.1. Compliance with Ethical and Regulatory Guidelines

This study will comply with the requirements that are enunciated in the European Clinical Trial Directive 2001/20/EC and in the US CFR.

14.2. Institutional and Ethics Review

This study will be conducted in full compliance with the IRB regulations in 21 CFR 56 and/or the European Clinical Trial Directive 2001/20/EC. Before enrollment of patients into the study, the protocol and informed assent (for patients, if applicable) and informed consent (for parents/legal guardians) documents will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol will be subjected to the same IRB/IEC and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the IP during the study. IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB/IEC and the regulatory authority should be retained in the study regulatory files.

14.3. Informed Consent/Assent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent from each patient, or patient's parent(s) or legal guardian(s), if applicable, and written assent from each patient, if applicable, must be obtained before any study-specific screening or baseline period evaluations are performed. One copy of the signed informed consent/assent documents will be given to the patient; the Investigator will retain the original copies of these documents.

The informed consent/assent documents, as prepared by the Sponsor or designee, must be reviewed and approved by the IRB/IEC and regulatory authorities, as applicable, before initiation of the study. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in the 21 CFR 50.25.

14.4. Compliance with the Protocol

All processes and procedures defined in this protocol will be adhered to. Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed by the Investigator as crucial for the safety and wellbeing of that patient may be instituted for that patient only and documented as deviations. The Investigator will contact the medical monitor as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB/IEC; however, the IRB/IEC and Medical Monitor must be notified in writing as soon as possible in accordance with the IRB/IEC policies after the departure has been made.

14.5. Confidentiality

14.5.1. Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, with the exception of information that is required by law or regulations to be disclosed to the IRB/IEC, the patient's parent(s) or legal guardian(s) or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act (HIPAA) standards and/or European standards.

14.5.2. Patient Confidentiality

The anonymity of participating patients will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. Patients may be referenced by their initials and an assigned patient identification number on the CRFs and other data collected by the Sponsor. The Investigator must maintain all documents related to the study that identify the patient (e.g. the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB/IEC, the study monitor, or the Sponsor or its representatives.

15. STUDY DOCUMENTATION AND GENERAL INFORMATION

15.1. Essential Study Documents

Essential study documents are among the critical documents required before study enrollment is to occur. Essential documents, as well as supplemental information such as the Investigator's Brochure, Pharmacy Manual, CRF Completion Guidelines, final protocol, as specified in the Clinical Operations Manual and/or Regulatory Binder, must be kept on-site in a designated study site file.

The study site files will also contain, including but not limited to, patient accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB/IEC correspondence, deviations, biological sample records, and SAE and Investigational New Drug (IND) safety reports/Safety Alert Letters.

15.2. General Information

The Investigator should refer to the current Investigator's Brochure along with subsequent Safety Alert Letters, the Clinical Study Operations Manual, Pharmacy Manual, Laboratory Manual, CRF Completion Guidelines, and all other study-specific information that is provided during the study initiation visit or by the study monitor.

15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics, Inc. However, at the conclusion of this clinical study, a clinical study report will be prepared. In addition, a manuscript will be prepared for publication in a reputable scientific journal under the direction of the Sponsor. Sarepta Therapeutics, Inc. will publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by Sarepta Therapeutics, Inc., as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov. After completion of the study, results will be disseminated through ClinicalTrials.gov.

15.4. Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the IP, the Investigator, clinical site pharmacist or pharmacy designee should contact the Sponsor or designated contract research organization (CRO).

16. LIST OF REFERENCES

Aartsma-Rus A, Fokkema I, Verschuuren J, Ginjaar I, van Deutekom J, van Ommen GJ, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. Hum Mutat. 2009 Mar;30(3):293-9.

Bushby KM and Gardner-Medwin D. The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy. I. Natural history." J of Neurol. 1993;240(2):98-104.

Beenakker, EA, Fock JM, et al. Intermittent prednisone therapy in Duchenne muscular dystrophy: a randomized controlled trial. Archives of Neurol. 2005;62(1):128-32.

Biggar WD, Harris VA, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscular Dis. 2006 Apr;16(4):249-55.

Brooke MH, Fenichel, GM, Griggs RC, Mendell JR, Moxley R, Miller JP, et al. Clinical Investigation in Duchenne dystrophy: 2. Determination of the "power" on therapeutic trials based on the natural history. Muscle and Nerve. 1983;6:91-103.

Brooke MH, Fenichel GM, Griggs RC, Mendell JR, Moxley R, Florence J, et al. Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. Neurol. 1989 Apr;39(4):475-81.

Cacchiarelli D, Legnini I, Martone J, Cazzella V, D'Amico A, Bertini E, Bozzoni. miRNAs as serum biomarkers for Duchenne muscular dystrophy. EMBO Mol Med. 2011;3(5):258-65.

CDC-MMWR. Prevalence of Duchenne/Becker Muscular Dystrophy Among Males Aged 5-24 Years – Four States, 2007. 2009;1119.

Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscular Dis. 2002 Dec;12(10):926-9.

Emery, AE. Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscular Dis. 1991;1(1):19-29.

Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. Dev Med Child Neurol. 2004;46:475-480.

Kohler M, Clarenbach CF, Bahler C, Brack T, Russi EW, Bloch KE. Disability and survival in Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry. 2009 Mar;80(3):320-5.

Lowes LP, Alfano LN, Yetter BA, Worthen-Chaudhari L, Hinchman W, Savage J, et al. Proof of concept of the ability of the kinect to quantify upper extremity function in dystrophinopathy. PLoS Curr. 2013 Mar 14

Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2004;(2):CD003725.

Mayhew A, Mazzone ES, Eagle M, Duong T, Ash M, Decostre V, et al. Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. Dev Med Child Neurol. 2013;55(11):1038-45.

Nadarajah VD, van Putten M, Chaouch A, Garrood P, Straub V, Lochmüller H, et al. Serum matrix metalloproteinase-9 (MMP-9) as a biomarker for monitoring disease progression in Duchenne muscular dystrophy (DMD). Neuromuscul Disord. 2011 Aug;21(8):569-78.

Pradhan, SD, Ghosh D, Srivastava NK, Kumar A, Mittal B, Pandey CM, et al. Prednisolone in Duchenne muscular dystrophy with imminent loss of ambulation. J Neurol. 2006;253(10):1309-16.