CLINICAL STUDY PROTOCOL

DRUG:	Eteplirsen (Eteplirsen Injection)
STUDY NUMBER:	4658-203
STUDY TITLE:	An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-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):	Version 3, Amendment 2 (08 June 2017)
REPLACES VERSION (DATE):	Version 2, Amendment 1 (20 January 2015)

[redacted]

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-Stage Duchenne Muscular Dystrophy
Study No:	4658-203, Amendment 2
Current Version Date:	08 June 2017

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.

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, MD MS

Date

08 June 2017

[redacted]

INVESTIGATOR'S AGREEMENT

I have read Study No. 4658-203 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	PPD 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, Multi-Center Study to Evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-Stage Duchenne Muscular Dystrophy	
PROTOCOL NUMBER: 4658-203	
PHASE OF STUDY: Phase 2	
INVESTIGATOR STUDY SITES: This study will be conducted at approximately 15 study sites in the United States.	
OBJECTIVES: The primary objective of this study is to evaluate the safety and tolerability of eteplirsen in patients with Duchenne muscular dystrophy (DMD) between 4 and 6 years of age who are amenable to exon 51 skipping The secondary objective is to evaluate the effect of eteplirsen on dystrophin expression as measured by dystrophin quantification by Western blot and dystrophin intensity levels determined by immunofluorescence on-treatment as compared to pre-treatment biopsied skeletal muscle tissue. CCI [redacted] The pharmacokinetic (PK) objective is to evaluate the pharmacokinetic profile of eteplirsen in this age group.	
METHODOLOGY: This is an open-label, multi-center study to evaluate the safety and tolerability of eteplirsen in patients 4 to 6 years of age with genotypically confirmed DMD with genetic mutations amenable to treatment by exon 51 skipping. An untreated control group (DMD patients not amenable to exon 51 skipping) will be enrolled to further evaluate the natural history of DMD in this patient population. Patients will be evaluated for inclusion during a Screening/Baseline period of up to 5 weeks. Eligible patients for the eteplirsen-treated group will receive once weekly intravenous (IV) infusions of 30 mg/kg eteplirsen for up to 96 weeks. An extension to the dosing period may be considered prior to the end of the 96-week planned dosing period. Eligible patients for the untreated group (eg, deletions of exons 44, 45, or 53) will not receive treatment with eteplirsen. Untreated patients will undergo select safety, functional, and laboratory assessments but will not provide blood samples for PK determination and will not undergo muscle biopsy procedures. Safety will be assessed through the collection of adverse events (AEs)/serious AEs (SAEs), laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations throughout the study. Upon qualification for the study, patients enrolled into the eteplirsen-treated group will undergo the baseline assessments including a muscle biopsy, which may occur at a different study site (denoted as the surgical unit) than where patients will undergo infusions and study assessments (denoted as the infusion site). Eteplirsen-treated patients will be randomized to a second muscle biopsy scheduled at Week 48 or Week 96. CCI [redacted]	

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

CCI [redacted]

Blood samples for population PK estimation will be collected from all eteplirsen-treated patients. Blood samples for serial PK estimation will be collected at select sites.

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

DURATION OF STUDY:

Screening/Baseline Period: Up to 5 weeks

Treatment Period: Up to 96 weeks

Safety Follow-up period: Four weeks following Week 96 or early discontinuation

Total duration of patient participation: Approximately 105 weeks

NUMBER OF PATIENTS: Up to 40 patients will be included in this study: approximately 20 patients in the eteplirsen-treated group (those amenable to exon 51 skipping) and up to 20 in the untreated control group (those not amenable to exon 51 skipping).

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 and meet one of the following criteria:
   - Have an out-of-frame deletion amenable to exon 51 skipping (eg, 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 deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing. These patients will be enrolled into the eteplirsen-treated group.
   - Have a deletion mutation that is not amenable to correction by exon 51 skipping as documented by a genetic report from an accredited laboratory confirming deletion endpoints by MLPA or sequencing. These patients will be enrolled into the untreated group.
2. Be 4 to 6 years of age, inclusive, at the Screening visit.
3. Has been on a stable dose of oral corticosteroids for at least 12 weeks prior to study drug administration *and* the dose is expected to remain constant (except for modifications to accommodate changes in weight) for at least the first 12 weeks of the study OR has not received corticosteroids for at least 12 weeks prior to study drug administration and does not expect to start corticosteroids within the first 12 weeks of eteplirsen dosing.
4. Have intact right and left biceps muscles or 2 alternative upper arm muscle groups (eteplirsen-treated patients only).
5. Have a parent(s) or legal guardian(s) who is able to understand and comply with all the study requirements.
6. Have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

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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 for DMD) within 12 weeks of study drug administration that might affect muscle strength or function (eg, growth hormone, anabolic steroids).
2. Previous or current treatment with any other experimental treatments within 12 weeks prior to study entry or participation in any other clinical trial within 6 months prior to study entry. (A patient may be enrolled in a concurrent non-interventional or observational study provided his participation does not interfere with this study.)
3. Major surgery within 3 months of study drug administration or planned major surgery for any time during this study.
4. Presence of other clinically significant (CS) illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease or malignancy.
5. Use of any systemic aminoglycoside antibiotic within 12 weeks of study drug administration or need for use of systemic aminoglycoside antibiotics or statins during the study.
6. Have a left ventricular ejection fraction (LVEF) of <50% based on the screening ECHO or QT interval corrected by Fridericia's formula (QTcF) ≥450 msec based on the screening ECG.
7. 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. Patients who seem unwilling or unable to comply with the study procedures, in the Investigator's opinion, are to be excluded.

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.

REFERENCE TREATMENT: None

CRITERIA FOR EVALUATION:

Safety Endpoints:

Incidence of the following for all patients in the study:

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

Secondary Endpoints:

Change from Baseline to Weeks 48 and 96 for the following:

- Dystrophin protein levels quantified by Western blot (eteplirsen-treated patients only)
- Dystrophin intensity as determined by immunofluorescence histochemistry (IHC) (eteplirsen-treated patients only)

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CCI [redacted]

Pharmacokinetic Endpoints:

- The PK of eteplirsen (eteplirsen-treated patients only) will be determined, as described below

Pharmacokinetics:

From the population PK samples, standard population PK parameters will be estimated. The effects of demographic characteristics, concomitant medications, laboratory values, and other covariates on eteplirsen PK will be evaluated.

From the serial PK samples, the following pharmacokinetic parameters will be determined, as appropriate:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Area under the plasma concentration-curve (AUC)
- Apparent volume of distribution at steady state (V_{ss})
- Elimination half-life ($t_{½}$)
- Total clearance (CL)
- Mean residence time (MRT)

SAMPLE SIZE:

Sample size for this study is based upon qualitative considerations. No formal sample size calculation has been made. The selected sample size is considered sufficient to provide initial safety evaluation of eteplirsen in the studied population; to provide adequate data to allow for estimation of PK parameters; and to provide biological proof-of -concept of exon skipping by eteplirsen in this age group.

STATISTICAL METHODS:

Safety Analyses

Treatment-emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT) for the eteplirsen-treated group. Adverse events since study enrollment will be summarized in the same fashion for the untreated group. For all AE tables, the number and percentage

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of patients reporting AEs will be grouped by the most current version of 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 specific visit, as well as the change from Baseline to that visit, will also be displayed. All safety data will be presented in data listings.

Efficacy Analyses

Analyses of Secondary Endpoints: The analysis of change from Baseline to Weeks 48 and 96 in the dystrophin protein levels quantified by Western blot (eteplirsen-treated patients only) will be based on a 1-sample permutation t-test for each time point. Change from Baseline to Weeks 48 and 96 in dystrophin intensity as determined by IHC will be analyzed similarly.

CCI [redacted]

Pharmacokinetic Analyses

Individual plasma levels of eteplirsen will be listed with the corresponding time related to eteplirsen administration, and summary statistics will be generated by per-protocol time of collection.

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

Plasma concentration-time data of eteplirsen will be used to perform a future population PK analysis using nonlinear mixed-effects modeling. Data may be combined with those of completed studies to support a relevant structural model.

2. SCHEDULE OF EVENTS FOR ETEPLIRSEN-TREATED PATIENTS

Study Period	Screening	Baseline[a]	Treatment Period												
Week	**Up to 5 weeks prior to Week 1**		**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Informed Consent	X														
Inclusion/Exclusion[b]	X	X	X												
Randomization[c]		X	X												
Medical History	X														
Full Physical Exam	X		X	X		X			X						X
Brief Physical Exam					X		X	X		X	X	X	X	X	
Vital signs	X	X	Weekly[d]												
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Lab Assessments	X	X[e]	X[f]	X[f]	X[f]	X[f]			X[f]			X[f]			X[f]
CCI [redacted]															
Whole Blood (DMD Genotyping and CCI [redacted])	X														
Height and Ulnar Length	X								X						X
Population PK[h]			X			X[i]			X			X[i]			X
Serial PK[j]					X										
CCI [redacted]															

Study Period	Screening	Baseline[a]	Treatment Period												
Week	**Up to 5 weeks prior to Week 1**		**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
ECG	X[k]								X[l]						X[l]
ECHO	X[k]								X[l]						X[l]
CCI [redacted]															
Muscle Biopsy[n]		X													X
Study Drug Infusion			Weekly (Infusion Site)												
Conmed/Therapy	Continuous														
AE Assessment	Continuous														

[a] For patients whose infusion site is the same as their surgical unit, Baseline visit may be performed on the same day as the Week 1 visit.
[b] Eligibility will be assessed during Screening and confirmed by the Infusion Site at the Baseline visit. Eligibility will be reconfirmed at Week 1 based on all available data including safety laboratory assessments.
[c] Upon qualification for the study during the Baseline visit, patients will be randomized to a muscle biopsy schedule.
[d] Patients will have vital signs measured on infusion days 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 reduced to pre-infusion and 30 minutes after the end of the infusion.
[e] Blood samples for the safety laboratory assessments must be obtained within 3 weeks prior to Week 1, and results must be available prior to dosing at Week 1. If more than 3 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, it must be repeated. If less than 3 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.
[f] Blood samples for safety laboratory assessments must be obtained prior to infusion.
CCI [redacted]
[h] Population PK blood samples will be taken prior to the beginning of the infusion and approximately 5 to 10 minutes after the completion of the infusion.
[i] Additional population PK blood samples collected approximately 1 to 2 hours after the completion of the infusion.
[j] Blood samples for serial PK sampling will be collected from some patients at select sites as follows: pre-dose (within 30 minutes prior to the start of infusion), and post-infusion at 5, 15, 30, 60, and 90 minutes, and 2, 5, 8, 12, 16, and 24 hours after the completion of study drug infusion.
[k] Screening ECG and ECHO may be performed at any time during the Screening period and results must be available on Day 1, prior to dosing.
[l] ECG and ECHO may be performed within ±2 weeks and should be performed at the same time of day for each visit during the course of the study.
CCI [redacted]
[n] Procedure will occur at the surgical unit. The biopsies at Weeks 48 and 96 must occur within 2 to 14 days of the visit. The muscle biopsy must occur after the clinical evaluation.

(table continued)

Study Period	Treatment Period (Continued)												End of Study
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**
Informed Consent													
Inclusion/Exclusion[b]													
Randomization[c]													
Medical History													
Full Physical Exam						X						X	
Brief Physical Exam	X	X	X	X	X		X	X	X	X	X		X
Vital signs	Weekly[d]												X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Lab Assessments						X[f]						X[f]	X
CCI													
Whole Blood (DMD Genotyping and CCI)													
Height and Ulnar Length						X						X	
Population PK[h]			X[i]			X			X[i]			X	
Serial PK[j]					X								
CCI													
ECG						X[l]						X[l]	
ECHO						X[l]						X[l]	
CCI													
Muscle Biopsy[n]												X	

Study Period	Treatment Period (Continued)												End of Study
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**
Study Drug Infusion	Once Weekly												
Conmed/Therapy	Continuous												
AE Assessment	Continuous												

[a] For patients whose infusion site is the same as their surgical unit, Baseline visit may be performed on the same day as the Week 1 visit.
[b] Eligibility will be assessed during Screening and confirmed by the Infusion Site at the Baseline visit. Eligibility will be reconfirmed at Week 1 based on all available data including safety laboratory assessments.
[c] Upon qualification for the study during the Baseline visit, patients will be randomized to a muscle biopsy schedule.
[d] Patients will have vital signs measured on infusion days 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 reduced to pre-infusion and 30 minutes after the end of the infusion.
[e] Blood samples for the safety laboratory assessments must be obtained within 3 weeks prior to Week 1, and results must be available prior to dosing at Week 1. If more than 3 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, it must be repeated. If less than 3 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.
[f] Blood samples for safety laboratory assessments must be obtained prior to infusion.
CCI [redacted]
[h] Population PK blood samples will be taken prior to the beginning of the infusion and approximately 5 to 10 minutes after the completion of the infusion.
[i] Additional population PK blood samples collected approximately 1 to 2 hours after the completion of the infusion.
[j] Blood samples for serial PK sampling will be collected from some patients at select sites as follows: pre-dose (within 30 minutes prior to the start of infusion), and post-infusion at 5, 15, 30, 60, and 90 minutes, and 2, 5, 8, 12, 16, and 24 hours after the completion of study drug infusion.
[k] Screening ECG and ECHO may be performed at any time during the Screening period and results must be available on Day 1, prior to dosing.
[l] The ECG and ECHO may be performed within ±2 weeks. The ECG and ECHO should be performed at the same time of day for each visit during the course of the study.
CCI [redacted]
[n] Procedure will occur at the surgical unit. The biopsies at Weeks 48 and 96 must occur within 2 to 14 days of the visit. The muscle biopsy must occur after the clinical evaluation.

3. SCHEDULE OF EVENTS FOR UNTREATED CONTROL PATIENTS

Study Period	Screening/Week 1[a]	Observation Period					
Week		**12**	**24**	**36**	**48**	**72**	**96/EOS**
Informed Consent	X						
Inclusion/Exclusion[b]	X						
Medical History	X						
Full Physical Exam	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Safety Lab Assessments	X	X	X	X	X	X	X
CCI							
Whole Blood (DMD Genotyping and CCI)	X						
Height and Ulnar Length	X		X		X		
CCI							
ECG[c]	X		X		X	X	X
ECHO[c]	X		X		X	X	X
CCI							
Conmed/Therapy	Continuous						
AE Assessment	Continuous						

[a] All assessments should be completed within a 5-week window for this visit with CCI occurring last within this window.
[b] For patients in the untreated control group, the date of the last Screening/Week 1 assessment (ie, CCI) will be used and recorded as the study start date.
[c] ECG and ECHO may be performed within +2 weeks and should be performed at the same time of day for each visit during the course of the study.
CCI

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5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2D	2 dimensional
6MWT	6-Minute Walk Test
AAOS	American Academy of Orthopaedic Surgeons
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMD	Becker muscular dystrophy
BMI	body mass index
BUN	blood urea nitrogen
CD	compact disc
CFR	Code of Federal Regulations
CK	creatine kinase
CL	total clearance
C_{max}	maximum plasma concentration
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
EOS	End of Study
GCP	Good Clinical Practices

Abbreviation	Definition
GGT	gamma-glutamyl transferase
HEENT	head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunofluorescence histochemistry
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	Interactive response technology
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]
mITT	modified Intent-to-Treat
CCI	[redacted]
MPLA	multiplex ligation-dependent probe amplification
CCI	[redacted]
mRNA	messenger ribonucleic acid
CCI	[redacted]
MRT	Mean residence time
NCS	not clinically significant
CCI	[redacted]
PDE-5	phosphodiesterase type 5
PK	pharmacokinetic
PMO	phosphorodiamidate morpholino oligomer
CCI	[redacted]
PT	Preferred Term

Abbreviation	Definition
QTcF	QT interval corrected by Fridericia's correction
RBC	red blood cells
RNA	ribonucleic acid
CCI [redacted]	[redacted]
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
CCI [redacted]	[redacted]
SUSARs	Suspected unexpected serious adverse reactions
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
US FDA	United States Food and Drug Administration
V_{ss}	apparent volume of distribution at steady state
WBC	white blood cell

6. INTRODUCTION

6.1. Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a degenerative neuromuscular disease with an X-linked recessive inheritance caused by mutations in the dystrophin gene, with a worldwide incidence of 1 in 5000 newborn boys, irrespective of geographical region, race, or population density (Zaharieva 2013; Mendell 2012; Moat 2013). The mutations that cause DMD typically disrupt the messenger ribonucleic acid (mRNA) reading frame and prevent production of dystrophin, a critically important part of the protein complex that connects the cytoskeleton of a muscle fiber to the cell membrane and extracellular matrix. In the absence of dystrophin, the stress of muscle contraction causes progressive muscle damage that ultimately involves all muscles, including skeletal, smooth, and cardiac. The clinical effect of this disrupted dystrophin reading frame is progressive worsening of muscle function and ultimately death.

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 (eg, 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).

6.2. 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 6-membered morpholinyl ring which replaces the 5-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 CCI [redacted]. As a result of the combination of the

morpholinyl rings and the uncharged linkages, PMOs have increased exon skipping activity and have decreased non-specific 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-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).

6.3. 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 these early clinical studies, a double-blind, placebo-controlled Phase 2 study (Study 4658-us-201) was initiated. This study randomized 12 patients aged 7 to 13 years to receive once weekly infusions of eteplirsen or placebo as follows: Group 1 received 50 mg/kg eteplirsen for 28 weeks (n=4); Group 2 received 30 mg/kg eteplirsen for 28 weeks (n=4); Group 3a received placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks (n=2); and Group 3b received placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks (n=2).

All 12 patients successfully completed Study 4658-us-201 and transitioned to an open-label extension study (Study 4658-us-202) where they continue to receive the same dose of eteplirsen (30 mg/kg or 50 mg/kg via weekly intravenous [IV] infusion) they were receiving at the end of Study 4658-us-201.

Study 4658-us-202 met its primary biological efficacy endpoint of increased novel dystrophin as assessed by immunofluorescence histochemistry (IHC) in muscle (biopsies at Week 48). Results through more than 2 years in Studies 4658-us-201 and 4658-us-202 have shown a continued stabilization of walking ability in continuously eteplirsen-treated patients evaluable on the 6-minute walk test (6MWT). At 120 weeks, patients in the 30 mg/kg and 50 mg/kg continuous-eteplirsen cohorts who were able to perform the 6MWT (n=6, modified Intent-to-Treat [mITT]) experienced a decline of 13.9 meters (<5%) from baseline in walking ability. (Note that 2 DMD boys lost their ambulation within the first month in Study 4658-us-201 due to disease progression. These boys were identical twins close to 10 years old who were excluded from the mITT population.) A statistically significant treatment benefit of 64.9 meters ($p \leq 0.006$) was observed for this group as compared to the placebo/delayed-treatment cohort (n=4), which initiated treatment at Week 25 following 24 weeks of placebo. After experiencing a substantial decline earlier in the study, this placebo/delayed-treatment cohort also demonstrated stabilization

in walking ability for more than 1.5 years (from Week 36 through Week 120), the period from which meaningful levels of dystrophin were likely produced, with a decline of 9.5 meters over this timeframe. These analyses were based on the maximum 6MWT score when the test was performed on 2 consecutive days.

No patient has withdrawn from Study 4658-us-202 due to an adverse event (AE). Through 120 weeks, eteplirsen has continued to be well tolerated, and there have been no reported clinically significant treatment-related AEs and no treatment-related serious adverse events (SAEs). In addition, there have been no treatment-related hospitalizations or discontinuations.

Refer to the Investigator's Brochure for further details on the nonclinical and additional clinical data for eteplirsen.

6.4. Rationale for the Current Study

The purpose of this study is to evaluate the safety of eteplirsen over 2 years of dosing in patients between 4 to 6 years of age, inclusive, with genetic mutations amenable to treatment by exon 51 skipping In addition, this study will enroll an untreated control group (DMD patients not amenable to exon 51 skipping) to further evaluate the natural history of DMD in this patient population.

7. STUDY OBJECTIVES

7.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of eteplirsen in patients with DMD between 4 and 6 years of age who are amenable to exon 51 skipping.

7.2. Secondary Objective

The secondary objective is to evaluate the effect of eteplirsen on dystrophin expression as measured by dystrophin quantification by Western blot and dystrophin intensity levels determined by immunofluorescence on-treatment as compared to pre-treatment biopsied skeletal muscle tissue.

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7.4. Pharmacokinetic Objective

The pharmacokinetic (PK) objective is to evaluate the pharmacokinetic profile of eteplirsen in this age group.

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is an open-label, multi-center study to evaluate the safety and tolerability of eteplirsen in patients 4 to 6 years of age with genotypically confirmed DMD with genetic mutations amenable to treatment by exon 51 skipping. In addition, this study will enroll an untreated control group (DMD patients not amenable to exon 51 skipping) to further evaluate the natural history of DMD in this patient population.

All patients will be evaluated for inclusion during a Screening/Baseline period. Written informed consent from the parent/legal guardian to participate in the study must be obtained prior to beginning any study-related procedures. Once eligibility is confirmed, all patients will undergo Screening Assessments as indicated in Sections 2 and 3 (Schedule of Events).

For patients in the eteplirsen group, blood samples collected at the Screening Visit for the safety lab assessments must be obtained within 3 weeks prior to the Week 1 visit, and results must be available prior to dosing at Week 1.

- However, if more than 3 weeks have elapsed since the collection of blood samples for the Screening safety lab assessments, it must be repeated.
- If less than 3 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 Week 1 assessments as indicated in Section 2.

Starting at Week 1, patients amenable to exon 51 skipping (treated patients) will receive once weekly IV infusions of 30 mg/kg eteplirsen for up to 96 weeks. An extension to the dosing period may be considered prior to the end of the 96-week planned dosing period.

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

Upon qualification for the study, patients enrolled into the eteplirsen group will undergo the baseline assessments including a muscle biopsy, which may occur at a different study site (denoted as the surgical unit) than where patients will undergo infusions and study assessments (denoted as the infusion site). Eteplirsen-treated patients will be randomized to a second muscle biopsy scheduled at Week 48 or Week 96. CCI [redacted] CCI [redacted]

Blood samples for population PK estimation will be collected from all eteplirsen-treated patients. Blood samples for serial PK estimation will be collected at select sites.

Following the end of the weekly infusions, patients will be required to return to the study site for End of Study safety evaluations. The total duration including Screening, Treatment, and Follow-up periods is approximately 105 weeks.

Patients in the untreated control group will undergo select safety, functional, and laboratory assessments over the course of the study but will not provide blood samples for PK determination and will not undergo muscle biopsy procedures. See Section 3 for the timing of applicable assessments for the untreated control group.

Refer to Section 11 for the detailed list of study assessments.

8.2. 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 6.3, these studies assessed the efficacy, safety, tolerability, and PK of 2 eteplirsen doses (50 mg/kg 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 2 doses tested in this study. Therefore, the lower dose was selected as the more conservative choice, because patients would presumably receive this drug as a life-long treatment.

8.3. Study Endpoints

8.3.1. Safety Endpoints

Incidence of the following (all patients in the study):

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

8.3.2. Secondary Endpoints

Change from Baseline to Weeks 48 and 96 for the following:

- Dystrophin protein levels quantified by Western blot (eteplirsen-treated patients only)
- Dystrophin intensity as determined by IHC (eteplirsen-treated patients only)

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- [redacted]
- [redacted]
- [redacted]

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- [redacted]

8.3.4. Pharmacokinetic Endpoints

From the population PK samples (eteplirsen-treated patients only), standard population PK parameters will be estimated. The effects of demographic characteristics, concomitant medications, laboratory values, and other covariates on eteplirsen PK will be evaluated.

From the serial PK samples, the following pharmacokinetic parameters will be determined, as appropriate:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Area under the plasma concentration-curve (AUC)
- Apparent volume of distribution at steady state (V_{ss})
- Elimination half-life ($t_{½}$)
- Total clearance (CL)
- Mean residence time (MRT)

8.4. Discussion of Study Design

This is an open-label study to provide safety data on eteplirsen in patients with DMD who are between 4-6 years of age. The primary focus of the study is safety; however, muscle biopsies are being performed and analyzed from all subjects to provide data about the effect of eteplirsen on dystrophin levels in this young patient population. CCI [redacted]

CCI Additionally, pharmacokinetic samples are being collected to provide information about the standard PK parameters for eteplirsen in this age group as well as to provide additional data for the population PK model.

The 96-week treatment duration of the study provides sufficient follow-up time to obtain safety data in this population.

An untreated group of DMD patients not amenable to exon 51 skipping (eg, those with confirmed deletions of exons 44, 45, or 53) have been included as a control group. These patients will not receive eteplirsen and will not undergo muscle biopsy procedures nor will they provide blood samples for PK determination. Patients in this untreated group will be followed for the entire study duration and will undergo select safety, functional, and laboratory assessments. These untreated patients are being enrolled to further evaluate the natural history of DMD in this patient population.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Number of Subjects

Up to 40 patients will be enrolled in this study: approximately 20 patients in the eteplirsen-treated group (those amenable to exon 51 skipping) and up to 20 in the untreated control group (those not amenable to exon 51 skipping).

9.2. Patient Inclusion Criteria

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

1. Be a male with DMD and meet one of the following criteria:
   - Have an out-of-frame deletion amenable to exon 51 skipping (eg, 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 deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing. These patients will be enrolled into the eteplirsen-treated group.
   - Have a deletion mutation that is not amenable to correction by exon 51 skipping as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing. These patients will be enrolled into the untreated group.
2. Be 4 to 6 years of age, inclusive, at the Screening visit.
3. Has been on a stable dose of oral corticosteroids for at least 12 weeks prior to study drug administration *and* the dose is expected to remain constant (except for modifications to accommodate changes in weight) for at least the first 12 weeks of the study OR has not received corticosteroids for at least 12 weeks prior to study drug administration and does not expect to start corticosteroids within the first 12 weeks of eteplirsen dosing.
4. Have intact right and left biceps muscles or 2 alternative upper arm muscle groups.
5. Have a parent(s) or legal guardian(s) who is able to understand and comply with all the study requirements.
6. Have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

9.3. 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 for DMD) within 12 weeks of study drug administration that might affect muscle strength or function (eg, growth hormone, anabolic steroids).
2. Previous or current treatment with any other experimental treatments within 12 weeks prior to study entry or participation in any other clinical trial within 6 months prior to

study entry. (A patient may be enrolled in a concurrent non-interventional or observational study provided his participation does not interfere with this study.)

3. Major surgery within 3 months of study drug administration or planned major surgery for any time during this study.
4. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease or malignancy.
5. Use of any systemic aminoglycoside antibiotic within 12 weeks of study drug administration or need for use of systemic aminoglycoside antibiotics or statins during the study.
6. Have a left ventricular ejection fraction (LVEF) of <50% based on the screening ECHO or QT interval corrected by Fridericia's formula (QTcF) ≥450 msec based on the screening ECG.
7. 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. Patients who seem unwilling or unable to comply with the study procedures, in the Investigator's opinion, are to be excluded.

9.4. Completion of a Subject's Participation in the Study

The length of a patient's participation will be from the time the informed consent form is signed until completion of the End of Study (Week 100) assessments for eteplirsen-treated patients or until Week 96 for untreated control patients.

9.5. Patient Withdrawal Criteria

Any patient can decide to withdraw from study participation at any time for any reason. In addition, the 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, in consultation with the Sponsor's medical monitor. Reasons for study withdrawal include but are not limited to:

- The patient was erroneously included in the study (ie, was found to not have 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.

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

Patients who receive at least 1 dose of eteplirsen who withdraw from the study within 4 weeks from their last functional assessment visit will be asked to return to the study site to complete an End of Study (EOS) visit (Week 100, Section 2) within 4 weeks after their last dose.

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Patients who discontinue eteplirsen dosing at Week 96, and transition to commercial drug, do not need to complete the End of Study visit assessments.

9.6. Study Discontinuation

If the Sponsor, the Investigator, the medical monitor, the study monitor, institutional review board/independent ethics committee (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
- A decision by the Sponsor to suspend or discontinue the study
- 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 Code of Federal Regulations (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 eteplirsen drug product to the Investigator and end the Investigator's participation in the study.

10. TREATMENT OF SUBJECTS

10.1. Investigational Drug Product – Eteplirsen Injection

10.1.1. Packaging and Labeling

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

The label text for the eteplirsen drug product 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.

10.1.2. Storage

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

10.2. Treatments Administered

Eligible patients in the eteplirsen-treated group will receive a weekly 30-mg/kg dose of eteplirsen as an IV infusion for up to 96 weeks.

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. It is recommended that a topical anesthetic cream (eg, 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 for the first year of treatment. If the patient has not experienced an infusion reaction after the first year of treatment, patients may be observed for at least 30 minutes following the end of each eteplirsen injection.

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.

10.2.1. Dose Modification, Reduction, or Delay

There is no provision for dose alteration in this study. If an eteplirsen-treated 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.

Patients who discontinue eteplirsen dosing at Week 96, and transition to commercial drug, do not need to complete the End of Study visit assessments.

10.3. Randomization and Blinding

This is an open-label study. DMD patients enrolled who are amenable to exon 51 skipping will receive weekly infusions of eteplirsen. DMD patients enrolled who are not amenable to exon 51 skipping will be included in the untreated control group.

Eteplirsen-treated patients will have a muscle biopsy performed at Baseline. Additionally, eteplirsen-treated patients will be randomly assigned through interactive response technology (IRT) to a second muscle biopsy to be performed at Week 48 or Week 96. The evaluation of the quantification of the dystrophin protein will be performed by personnel blinded to the time point of the patient's muscle biopsy (ie, pre- and on-treatment). For further details about this assessment refer to Section 11.4.1.

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Evaluation of CCI [redacted] CCI [redacted] CCI [redacted] assessors will be blinded to patient identity and study treatment.

10.4. Prior and Concomitant Medications

Oral corticosteroids, including, but not limited to, prednisolone and prednisone, for treatment of DMD may be required during the course of this study. Patients entering the study must have been on a stable dose of oral corticosteroids for at least 12 weeks prior to study drug administration with the expectation the dose is expected to remain constant (except for modifications to accommodate changes in weight) for at least the first 12 weeks of the study and to the completion of study to the degree that is clinically feasible.

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 angiotensin-converting enzyme (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 (eg, 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 (ie, 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, except for treatment of an acute condition, eg, poison ivy
- 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 phosphodiesterase type 5 (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). (The use of topical aminoglycosides is allowed.)
- Statins (unless discussed and agreed upon with the Investigator and Medical Monitor)

10.5. Treatment Compliance

Treatment compliance (eteplirsen-treated patients) will be assessed via compliance with scheduled weekly infusions.

11. STUDY ASSESSMENTS

Unless otherwise noted below, assessments described in this section apply to all patients in the study, eteplirsen-treated and untreated.

11.1. Study Schedule of Events

A detailed schedule of the study assessments and times for eteplirsen-treated patients is shown in Section 2. A schedule of assessments for the untreated control group is provided in Section 3.

11.2. Assessments at the Screening/Baseline Visits

11.2.1. Informed Consent

Written informed consent from parent/legal guardian(s) for all patients' participation in this study must be obtained prior to beginning any of the procedures for this study.

11.2.2. Medical History

Medical history will be obtained for all patients.

11.2.3. Blood samples for DMD Genotyping CCI

Blood samples for all patients will be obtained at Screening for confirmation of DMD genotyping. Eteplirsen-treated patients may start dosing based on local genotyping results provided that these results fulfill the required criteria described in Section 9.2; these 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. CCI

Patients in the untreated control group will also undergo genetic testing to confirm their DMD mutation (eg, deletions of exons 44, 45, or 53). Patients whose genotype is not verifiable will be excluded from continuing in this trial. CCI

11.3. Safety Assessments

11.3.1. Physical Examination

Physical examinations, full and brief, will be conducted at the time points specified in Section 2 for eteplirsen-treated patients. 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 (eteplirsen-treated patients only) will include examination of general appearance, HEENT, heart, lungs, chest, abdomen, and skin.

Untreated patients will have a full physical examination performed at time points specified in Section 3.

11.3.2. Vital Signs and Weight

For eteplirsen-treated patients, vital signs (blood pressure, heart rate, respiration, and 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 reduced to pre-infusion and 30 minutes after the end of 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.

Patients in the untreated control group will have their vital signs and weight recorded at the time points specified in Section 3.

11.3.3. Clinical Laboratory Evaluations

The following routine clinical laboratory tests will be collected for eteplirsen-treated patients 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), lactate 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.

Patients in the untreated control group will also undergo laboratory testing at the time points specified in Section 3.

11.3.4. Height and Ulnar Length

Height and ulnar length will be measured at the time points specified in Sections 2 and 3.

Height should be measured with shoes off.

For ulnar length, 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).

11.3.5. Electrocardiogram

Twelve-lead ECGs will be obtained at the time points specified in Sections 2 and 3. 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.

11.3.6. Echocardiogram

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in Sections 2 and 3. 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.

11.3.7. 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 parent or legal guardian signs the informed consent form. Information on any physiotherapeutic intervention must be collected in detail for this study.

11.3.8. Adverse Events

The collection of AEs is described in Section 12.

11.4. Efficacy Assessments

11.4.1. Secondary Efficacy Assessment

Upon qualification for the study during the Baseline visit, patients in the eteplirsen group will undergo a muscle biopsy at Baseline and will be randomized to a second muscle biopsy schedule at either Week 48 (50%) or Week 96 (50%). The biopsies at Weeks 48 and 96 must occur within 2 to 14 days of the visit. The muscle biopsy must occur after the clinical evaluation.

The Baseline muscle biopsy will be obtained from 1 biceps brachii muscle and the subsequent muscle biopsy will be obtained from the contralateral muscle. A previously unbiopsied alternative upper arm muscle, such as the deltoid, may be used if the biceps brachii has been biopsied previously. If an alternative muscle group is used, the same contralateral muscle will be biopsied at the subsequent muscle biopsy as well.

Muscle biopsy samples will be collected at the Surgical Units and will be sent to a designated laboratory for analysis. All analyses related to quantification of the dystrophin protein as measured by dystrophin quantification by Western blot and dystrophin intensity levels determined by immunofluorescence will be performed by personnel blinded to the time point of the patient's muscle biopsy (ie, pre- and on-treatment). Details are provided in the Laboratory Manual.

Additional assessments completed on the muscle biopsy samples are presented in Section 11.4.2.5.

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11.5. Pharmacokinetic Assessments

Blood samples for assessing plasma drug concentrations will be obtained from eteplirsen-treated patients, as specified in Section 2. Refer to the Study Laboratory Manual for sample processing. Plasma samples will be analyzed to determine concentrations of eteplirsen.

11.5.1. Population PK Sampling

Population PK blood samples will be obtained from eteplirsen-treated patients at the time points specified in Section 2 prior to the beginning of the infusion and approximately 5 to 10 minutes after the completion of the infusion. Additional population PK blood samples will be collected at the time points specified in Section 2 approximately 1 to 2 hours after the completion of the infusion.

11.5.2. Serial PK Sampling

Blood samples for serial PK sampling will be collected from some eteplirsen-treated patients at select sites at the time points specified in Section 2 as follows: pre-dose (within 30 minutes prior to the start of infusion), and post-infusion at 5, 15, 30, 60, and 90 minutes, and 2, 5, 8, 12, 16, and 24 hours after the completion of study drug infusion.

12. ADVERSE EVENTS

12.1. 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 the End of Study visit (or early termination from the study) will be recorded in each individual patient's CRF. For eteplirsen-treated patients who prematurely discontinue the study (see Section 9.5), 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 9.5), the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly/probably or definitely related to the IP (Section 12.3.1) or is possibly/probably or definitely related to a study procedure (Section 12.3.2), then the event and any known details must be reported promptly to the Sponsor.

12.2. Definition of Adverse Events

12.2.1. 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. AEs 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.

12.2.2. 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, ie, 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.

12.3. Classification of Adverse Events

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

12.3.1. 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.

12.3.2. 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

12.3.3. 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 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.

12.3.4. Severity of Adverse Events

Note that severity is not the same as "seriousness," which is defined in Section 12.2.2 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.

12.3.5. Outcome

For eteplirsen-treated patients, all AEs will be followed for 4 weeks after the last dose of investigational drug product. Serious AEs will be followed until resolution or until the condition stabilizes or returns to baseline status or until no further follow-up is expected. The Investigator will record all information regarding to patient outcome for each AE or SAE.

For untreated control patients, AE/SAEs will be followed until resolution to the extent possible.

12.3.6. 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.

12.3.7. 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.

12.3.8. 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(s) per the requirements of the concerned competent bodies. SUSARs will also be reported to study Investigators.

12.4. Recording Adverse Events

All AEs/SAEs experienced from the time of informed consent 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.

12.5. 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 12.2.2. Refer to the SAE Reporting Plan for further details on the transmission of SAE Reports.

12.6. Special Situations

12.6.1. Overdose

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.

12.6.2. 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.

12.6.3. 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

12.6.4. 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

13. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

13.1. 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.

13.2. 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).

13.3. 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.

14. STATISTICS

14.1. 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 non-missing values. 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. Inferential statistics, if calculated, will be used for descriptive purposes only.

14.2. Determination of Sample Size

Sample size for this study is based upon qualitative considerations. No formal sample size calculation has been made. The selected sample size is considered sufficient to provide initial safety evaluation of eteplirsen in the studied population; to provide adequate data to allow for estimation of pharmacokinetic parameters; and to provide biological proof-of -concept of exon skipping by eteplirsen in this age group.

14.3. Analysis Sets

The Safety set includes all patients who are enrolled in the eteplirsen group and receive at least 1 dose of eteplirsen as well as all patients who are enrolled in the untreated group who have at least 1 safety assessment post-enrollment.

Additional analysis sets will be defined in the SAP.

14.4. 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 (eg, inclusion/exclusion, prohibited therapies).

14.5. 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 will be summarized. Demographic data and baseline characteristics will be presented in data listings.

14.6. Medical History

Medical history will be presented in data listings.

14.7. 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 for all eteplirsen-treated patients. Dosing information will be provided in a data listing.

14.8. Safety Analyses

14.8.1. Safety Variables

Incidence of:

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

14.8.2. Safety Analysis

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.

14.8.2.1. Adverse Events

For eteplirsen-treated patients, 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. 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
- Treatment-emergent SAEs
- Death
- Overdose

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

For untreated patients, AEs and SAEs that first occur or worsen in severity after the study enrollment will be summarized in the same fashion as the TEAEs and treatment-emergent SAEs for the eteplirsen-treated group. In addition, all SAEs, regardless of time of occurrence, will be summarized by SOC and PT.

For all patients, the following listings will be produced:

- All AEs, including non-treatment emergent AEs and TEAEs
- AEs leading to discontinuation
- SAEs

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

Vital signs, weight, and height/ulnar length will be presented by 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.

14.8.2.3. Clinical Laboratory Tests

Clinical chemistry, hematology, coagulation, and urinalysis will be presented by 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.

14.8.2.4. Electrocardiograms

The actual value and change from Baseline to each visit will be presented by 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.

14.8.2.5. Echocardiograms

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

14.8.2.6. Prior and Concomitant Medications and Physiotherapeutic Interventions

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

14.9. Efficacy Analysis

14.9.1. Efficacy Variables

14.9.1.1. Secondary Efficacy Endpoints

Change from Baseline to Weeks 48 and 96 for the following:

- Dystrophin protein levels quantified by Western blot (eteplirsen-treated patients only)
- Dystrophin intensity as determined by IHC (eteplirsen-treated patients only)

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14.9.2. Efficacy Analyses

14.9.2.1. Analyses of Secondary Efficacy Endpoints

The analysis of change from Baseline to Weeks 48 and 96 in dystrophin protein level as quantified by Western blot (eteplirsen-treated patients only) will be based on a 1-sample

permutation t-test for each time point. Change from Baseline to Weeks 48 and 96 in dystrophin intensity as determined by IHC will be analyzed similarly.

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[redacted]

[redacted]

[redacted]

14.10. PK Analysis

For eteplirsen-treated patients, individual plasma levels of eteplirsen will be listed with the corresponding time related to eteplirsen administration and summary statistics will be generated by per-protocol time of collection.

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

Plasma concentration-time data of eteplirsen will be used to perform a future population PK analysis using nonlinear mixed-effects modeling. Data may be combined with those of completed studies to support a relevant structural model.

14.11. Interim Analysis

No interim analysis is planned for this study.

14.12. Other Statistical Issues

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

15. SPECIAL REQUIREMENTS AND PROCEDURES

15.1. 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.

15.2. 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 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.

15.3. Informed Consent and Authorization for Use and Disclosure of Protected Health Information

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

The informed consent 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.

15.4. 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.

15.5. Confidentiality

15.5.1. 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.

15.5.2. Patient Anonymity

The anonymity of participating patients will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. Patients will 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 (eg, 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.

16. STUDY DOCUMENTATION AND GENERAL INFORMATION

16.1. 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 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 IND safety reports / Safety Alert Letters.

16.2. 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.

16.3. 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.

16.4. 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).

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