CLINICAL STUDY PROTOCOL

DRUG:	Eteplirsen (Eteplirsen Injection)
STUDY NUMBER:	4658-102
STUDY TITLE:	An Open-Label Safety, Tolerability, and Pharmacokinetics Study of Eteplirsen in Young Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping
EUDRACT Number:	2016-000951-29
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	Version 4, 07 February 2020
PRIOR VERSION DATE:	Version 1 (Original; 30 June 2016) Version 2, 09 January 2017 Version 3, 06 March 2017

the written authorization of the Sponsor, except to the extent necessary to obtain written informed consent from those individuals to whom the drug may be administered. These restrictions will continue to apply after the study has closed.

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	An Open-Label Safety, Tolerability, and Pharmacokinetics Study of Eteplirsen in Young Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping
Study No:	4658-102
Current Version Date:	07 February 2020

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) described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312; and the European Clinical Trial Directive 2001/20/EC and European Union (EU) Clinical Practice Directive 2005/28/EC; ICH E6 (R2) Good Clinical Practice Guideline.

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

[redacted]

11 Feb 2020

Date

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

INVESTIGATOR'S AGREEMENT

I have read the Study Protocol 4658-102 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	[redacted]	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Mobile Phone : [redacted] Email: [redacted]

1. SYNOPSIS

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

TITLE: An Open-Label Safety, Tolerability, and Pharmacokinetics Study of Eteplirsen in Young Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

Study Number: 4658-102

Phase of Study: Phase 2

INVESTIGATOR STUDY SITES: This multicenter study will be conducted at approximately 5 sites in the European Union.

OBJECTIVES:

Primary Objective

- To evaluate the safety and tolerability of eteplirsen administered once weekly by intravenous (IV) infusion in male Duchenne muscular dystrophy (DMD) patients ages 6 months to 48 months, inclusive.

Secondary Objective

- To determine the pharmacokinetics (PK) of eteplirsen at the 2-, 10-, 20-, and 30-mg/kg dose levels, administered once weekly by IV infusion in male DMD patients ages 6 months to 48 months, inclusive.

[redacted]

- [redacted]

METHODOLOGY:

This is a multicenter, open-label, dose-escalation study to evaluate the safety, tolerability, PK, and efficacy of once-weekly IV infusions of eteplirsen in approximately 12 male patients ages 6 months to 48 months (inclusive) who have genotypically confirmed DMD with a deletion mutation amenable to exon 51 skipping.

Screening

Patients will be evaluated for inclusion during the Screening Period of up to 2 weeks to ensure eligibility prior to dosing with eteplirsen. After obtaining informed consent, screening assessments will include a review of inclusion/exclusion eligibility criteria, demographics and medical history, previous and current medications, clinical safety laboratory testing (blood and urine samples), vital signs, physical examination (including height/length and weight), 12-lead electrocardiogram (ECG), and echocardiogram (ECHO). Blood samples for the screening clinical safety laboratory assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1. A blood sample to confirm DMD genotype will also be obtained. Patients not previously genotyped may be consented and have genotype performed as part of the study. Once the genotype is confirmed, all additional screening procedures will be performed 2 weeks from Week 1/Baseline. The sample for genotyping can be drawn at Screening or any time prior to the Week 2 visit so that total blood volume taken for the Screening visit does not exceed recommendations. A separate blood sample will be obtained for genotyping of latent transforming growth factor beta (TGF) binding protein 4 (LTBP4) and secreted phosphoprotein 1 (SPP-1); this may be drawn at any time during the dose-titration period. [redacted]

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

[redacted]

Treatment Period

Patients will be enrolled into 1 of 2 age cohorts. Cohort 1 will include approximately 6 patients ages 24 to 48 months old and Cohort 2 will include approximately 6 patients ages 6 to <24 months old. Cohort 1 will be enrolled first, and only after the first 3 patients in Cohort 1 have completed at least 12 infusions of eteplirsen and all available safety data have been reviewed will enrollment begin for patients in Cohort 2. An external Data Monitoring Committee (DMC) will review safety data at least weekly through the first 12 weeks of dosing for the first 3 patients of each age cohort. Reviews will be at least quarterly thereafter.

The dose-titration period will last 10 weeks overall (1 infusion/week) to slowly achieve the target dose of 30 mg/kg. Eteplirsen dosing will begin at 2 mg/kg for 2 weeks (Weeks 1 and 2) and will escalate to 4 mg/kg (Weeks 3 and 4), 10 mg/kg (Weeks 5 and 6), 20 mg/kg (Weeks 7 and 8), and 30 mg/kg (Weeks 9 and 10). Patients will continue to receive 30 mg/kg eteplirsen for the duration of the study. The duration of each patient's treatment in the study is expected to be at least 48 weeks (including the titration period), and patients may continue to receive treatment in the study for up to 96 weeksbased on the judgement of the Investigator. In addition, study drug may be interrupted or discontinued for specific safety reasons.

Safety will be regularly assessed throughout the study via the collection of adverse events (AEs), clinical safety laboratory tests (blood chemistry, hematology, renal function, coagulation, and urinalysis), ECGs, ECHOs, vital signs, and physical examinations. Specific laboratory assessments of interest include:

- Any ≥Grade 2 (moderate) or serious event without an alternative etiology that the Investigator deems is related to study drug
- Two consecutive drug-related serum creatinine levels ≥2 × upper limit of normal (ULN) without an alternative etiology
- A confirmed, unexplained, increase in gamma-glutamyl transferase (GGT) >3 × ULN and either an increase in bilirubin >2 × ULN or nascent prothrombin time >2 × ULN concurrently, without an alternative etiology

Plasma and urine samples for PK determination will be collected at Week 2 (2-mg/kg dose level), Week 6 (10-mg/kg dose level), Week 8 (20-mg/kg dose level) and at Weeks 10 and 24 (30-mg/kg dose level). Plasma samples will be collected pre-dose, immediately prior to the end of infusion (prior to flush) and approximately 1 to 3 hours and 6-8 hours after completion of study drug infusion. Urine PK samples will be collected over the first 4 hours after start of infusion.

[redacted]

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

[redacted]

End-of-Study Follow-up Visit

Approximately 4 weeks after the last eteplirsen infusion (regardless of the duration of the patient's participation in the study), patients will be required to return to the study site for safety evaluations. The safety follow-up visit will include clinical safety laboratory testing, vital signs, physical examination, and assessment of AEs and concomitant medications.

DURATION OF STUDY:

Screening Period: Up to 2 weeks

Treatment Period: At least 48 weeks (including the 10-week titration period) and continuing for up to 96 weeks

Safety Follow-up Period: Up to 4 weeks after the last infusion

Total Patient Participation: The duration of each patient's treatment in the study is expected to be at least 48 weeks, and patients may continue to receive treatment in the study for up to 96 weeks. Therefore, the overall duration of a patient's participation in the study, inclusive of the 2-week Screening Period and 4-week Follow-up Period, may be up to 101 weeks.

NUMBER OF PATIENTS: Approximately 12 patients will be enrolled in this study (approximately 6 patients in Cohort 1 and approximately 6 patients in Cohort 2).

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

A patient must meet all of the following criteria to be eligible to participate in this study:

1. Be a male between 6 months to 48 months of age, inclusive.
2. Have an established clinical diagnosis of DMD with a deletion mutation amenable to exon 51 skipping (eg, deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63).
3. Have a parent(s) or legal guardian(s) who is able to understand and comply with the study requirements and is willing to provide written informed consent for the patient to participate in the study.

Exclusion Criteria

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

1. Has received any pharmacologic treatment that might have an effect on muscle strength or function within 12 weeks prior to dosing at Week 1 (eg, growth hormone, anabolic steroids).
2. Has received previous or current treatment with any experimental treatment. Prior drisapersen therapy is permitted if a patient has not received drisapersen for 6 months prior to the Week 1 dose.
3. Has a clinically significant illness other than DMD, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease, or malignancy likely to impair the patient's ability to participate in this study.
4. Has a clinically significant laboratory abnormality that is either not expected or is of a greater severity than what is expected in DMD patients.
5. Has any other condition that, in the Investigator's opinion, could interfere with the patient's participation in the study.

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

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Eteplirsen drug product is supplied as a sterile, clear, colorless, phosphate-buffered saline solution in single-use, 2-mL vials each containing 2 mL of eteplirsen at 50 mg/mL. Eteplirsen will be administered once a week by IV infusion.

The starting dose is 2 mg/kg eteplirsen, with escalation to 4, 10, 20, and 30 mg/kg over the course of the dose-titration period.

REFERENCE TREATMENT: None

CRITERIA FOR EVALUATION:

Primary Endpoint

The primary endpoint is safety and tolerability of eteplirsen in this study population, as measured by:

- Incidence of AEs
- Abnormal changes from Baseline or clinically significant worsening of clinical safety laboratory abnormalities (hematology, chemistry, coagulation, and urinalysis)
- Abnormal changes from Baseline or worsening of vital signs
- Abnormal changes from Baseline or worsening of physical examination findings
- Abnormal changes from Baseline or clinically significant worsening of ECGs and ECHOs

Secondary Endpoint

The secondary endpoint is to determine the PK of eteplirsen by population PK methods, including assessment of the following PK parameters (if evaluable):

- Maximum plasma concentration (C_{max})
- Time of C_{max} (T_{max})
- Area under the concentration-time curve (AUC)
- Apparent volume of distribution at steady state (V_{ss})
- Clearance (CL)
- Elimination half-life ($t_{½}$)
- Amount of drug eliminated in urine (Ae%)

[redacted]

[redacted]

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

STATISTICAL METHODS:

Safety Analyses

Treatment-emergent adverse events (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term.
Non-treatment-emergent events will be recorded in the data listings. For all AE tables, the number and percentage of patients reporting AEs will be grouped by SOC and preferred term for each age cohort and overall. Multiple occurrences of the same AE (at the preferred term level) in the same patient will be counted only once in the frequency tables. If a patient experiences multiple episodes of the same event with different severity, the event with the maximum severity will be used to summarize AEs by severity (likewise for relationship). Treatment related TEAEs will be defined as those that the Investigator considers related to the investigational product.

Descriptive statistics for ECG, ECHO, vital signs, height/length, weight, and safety laboratory parameters will be displayed by visit for each age cohort and overall. Summary statistics for each parameter at specific time points, as well as the change from baseline to that time point, will also be displayed. All data will be presented in data listings. Clinically significant physical examination findings will be recorded as AEs.

Pharmacokinetic Analyses

Pharmacokinetic parameters of eteplirsen will be determined from plasma and urine concentration data obtained at the 2-, 10-, 20-, and 30-mg/kg dose levels. Individual plasma and urine levels of eteplirsen will be listed with the corresponding time relative to eteplirsen administration, and summary statistics will be generated by per-protocol time of collection. PK parameters for eteplirsen will be calculated using non-compartmental analysis and/or using population PK methodology, as appropriate. 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.

[redacted]

Interim Analysis

An interim analysis of the PK and safety data following completion of dose escalation for one or both age cohorts may be done.

2. SCHEDULE OF EVENTS

The schedule of study events is presented in Table 2.

Table 2: Schedule of Events: Screening through Week 48

Study Period	**Screening**	**Treatment Period: Dose Titration**											**Stable Dose Treatment Period**										
Visit/Week	**Up to -2 wks**	**1 BL**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48[a]**
Informed consent[b]	X																						
Inclusion/Exclusion eligibility	X	X																					
Demographics and medical history	X																						
Blood samples genotyping[b]	X																						
Clinical safety laboratory sample[c]	X		X		X				X				X				X			X			X
PK plasma and urine sampling[d]			X				X		X		X						X						
Vital signs[e]	X	X	On weekly infusion days																				
Weight[f]	X	X	Weekly																				
Urine dipstick testing			Weekly																				
Renal function blood tests[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative urine analysis[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (including height/length)[g]	X	X			X				X				X	X		X	X	X	X	X	X	X	X
[redacted]																							
12-lead ECG[i,k]	X								X				X				X			X			X
ECHO[i,k]	X								X				X				X			X			X
Eteplirsen dosing[l]		Weekly IV infusion											Weekly IV infusion										

		2 mg/kg	4 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg	30 mg/kg[l]
Concomitant medications	Continuous						
AE monitoring	Continuous						

Footnotes for Table 2 Scheduleof Events: Screening through Week 48

Abbreviations: AE = adverse event; [redacted]; BL = baseline; DMB = Duchenne muscular dystrophy; DNA = Deoxyribonucleic acid; ECG= electrocardiogram; ECHO = echocardiogram; IV= intravenous; LTBP4 = latent transforming growth factor beta binding protein 4; [redacted] PK = pharmacokinetic; SPP-1 = secreted phosphoprotein 1.

[a] Patients are considered completers for thepurpose of analysis once the Week 48 assessments havebeen completed. Patients may continue in the study up to and including 96 weeks; however, a Safety Follow-up visit will occur approximately 4 weeks after the last doseadministered rega rdless of the patient's duration in the study (see Table 3).

[b] Patients not previously genotyped may beconsented and havegenotypeperformed as part of the study. Oncethe genotype is con firmed, all additional screening procedures will be performed -2 weeks from Week 1/Baseline. Patients may be enrolled in the study based on historical DNA test results; however, a blood sample for DNA testing will be obtained on all patients to confirm DMD mutation(s). In addition, a second blood sample will be obtained for genotyping of LTBP4 and SPP-1. So that total blood volume taken for the Screening visit does not exceed recommendations, theblood sample for DMD genotyping may be drawn at any time prior to the Week 2 visit and theblood sample for LTBP4 and SPP-1 may be drawn at any timeduring the dose-titration period. If the confirmatory DNA sample is negative for DMD on any enrolled patient, that patient will be withdrawn from the study.

[c] Clinical safety laboratory assessments (blood chemistry [including liver function], renal function, hematology [including pla telets], and coagulation) must be obtained with results available within 2 weeks prior to dosing. (See Section 10.3.5 for the list of tests to be completed.)

[d] Pla sma PK samples will be collected pre-dose, immediately prior to the end of infusion (prior to flush) and approximately 1 -3 hours and 6-8 hours after completion of study drug infusion. Urine PK will be collected over the first 4 hours after start of infusion.

[e] Vital signs include blood pressure, heart rate, respiration, and temperature. On infusion days, vital signs will be measured within 60 minutes prior to infusion, within 5 minutes (±2) after the end of infusion, and at 30 minutes (±5), and 60 minutes (±10) after the end of the infusion. All assessments will be performed after patients have remained calm for 5 minutes. Pulse rate and respiratory rate should bemeasured over 1 minute.

[f] Weight will be measured prior to study drug infusions at thespecified visits.

[g] Height/length will be measured as part of every physical examination. The examination will include general appearance; head, ears, eyes, nose, and throat; heart; lungs; chest; abdomen; skin; lymph nodes; musculoskeletal; and neurological systems.

[h] [redacted]

[i] A 2-week window is allowed in the event thechild is unable to completethis assessment at a given visit.

[j] Only performed in patients 36 months of age and older

[k] [redacted]

[l] Patients should receiveeteplirsen once every 7 days starting on Study Week 1. A window of ±3 days from the scheduled dose is acceptable after thefirst infusion. Patients may not receive 2 separatedoses of eteplirsen within the same 60-hour period. The Medical Monitor should be contacted in the event of ≥2 consecutivemissed doses.

[m.] Renal function blood tests includecreatinine, blood urea nitrogen, and serum cystatin C.

[n.] Quantitativeurine analysis includes KIM-1 and urinalysis (pH, specific gravity, protein, glucose, ketones, cytology, and hemoglobin).

Table 3: Schedule of Events: Week 49 through Week 96 and End-of-Study Follow-up

Study Period	**Stable Dose Treatment Period**					
Visit/Week	**49**	**60**	**72**	**84**	**96/ET[a]**	**Safety F/U[b]**
Clinical safety laboratory sample[c]		X	X	X	X	X
Vital signs[d]	On weekly infusion days				X	X
Weight[e]	Weekly				X	X
Urine dipstick testing	Weekly					
Renal function blood tests[l]	X	X	X	X	X	
Quantitative urine analysis[m]	X	X	X	X	X	
Physical examination (including height/length)[f]		X	X	X	X	X
[redacted]						
12-lead ECG[h,j]		X	X	X	X	
ECHO[h,j]		X	X	X	X	
Eteplirsen dosing[k]	Weekly IV infusions[k]					
Concomitant medications	Continuous					X
AE monitoring	Continuous					X

Abbreviations: AE = adverse event; [redacted]; ECG= electrocardiogram; ECHO = echocardiogram; ET = early termination; F/U = follow up; [redacted]; IV = intravenous; [redacted]

[a] Early termination assessments are thesame as Week 96 assessments.

[b] A Safety Follow-up visit will occur approximately 4 weeks after the last infusion regardless of thepatient's duration in the study.

[c] Clinical safety laboratory assessments (blood chemistry [including liver function], hematology [including platelets], and coa gulation) will be obtained every 12 weeks after Week 48. (See Section 10.3.5 for the list of tests to be completed.)

[d] Vital signs include blood pressure, heart rate, respiration, and temperature. On infusion days, vital signs will be measured approximately 60 minutes prior to infusion and at 5 minutes(±2), 30 minutes (±5), and 60 minutes (±10) after the end of the infusion. If the patient has not experienced an infusion reaction after the first 48 weeks of treatment, vital signs may be limited to approximately 30 minutes prior to infusion and 30 minutes (±5) after theend of the infusion. All assessments will be performed after patients have remained calm for 5 minutes. Pulse rate and respiratory rate should be measured over 1 minute.

[e] Weight measured will be measured prior to study drug infusions at thespecified visits.

[f] Height/length will be measured as part of every physical examination. The examination will include general appearance; head, ears, eyes, nose, throat; heart; lungs; chest; abdomen; skin; lymph nodes; musculoskeletal; and neurological systems.

[g] [redacted]

[h] A 2-week window is allowed in the event thechild is unable to completethis assessment at a given visit.

[I] Only performed in patients 36 months of age and older.

[j] [redacted]

[k] Patients should receiveeteplirsen once every 7 days relative to the Study Week 1 date. A window of ±3 days from the scheduled doseis acceptable after the first infusion. Patients may not receive 2 separate doses of eteplirsen within thesame 60-hour period. The Medical Monitor should be contacted in the event of ≥2 consecutivemissed doses.

[l.] Renal function blood tests includecreatinine, blood urea nitrogen, and serum cystatin C.

[m.] Quantitative urine analysis includes KIM-1 and urinalysis (pH, specific gravity, protein, glucose, ketones, cytology, and hemoglobin).

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	6-minute walk test
AE	adverse event
Ae%	amount of drug eliminated in urine (expressed as % of dose administered)
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from Hour 0 to 24 hours postdose
[redacted]	[redacted]
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CBC	complete blood count
CK	creatine kinase
CL	clearance
CNS	central nervous system
C_{max}	maximum plasma concentration
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	Computed tomography
DMC	Data Monitoring Committee
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GGT	gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HEENT	head, ears, eyes, nose, throat
[redacted]	[redacted]

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous, intravenously
KIM-1	kidney injury molecule 1
LTBP4	latent transforming growth factor beta binding protein 4
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PMO	phosphorodiamidate morpholino oligomers
[redacted]	[redacted]
RBC	Red blood cell(s)
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMA	spinal muscular atrophy
SPP-1	secreted phosphoprotein 1
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
t½	elimination half life
TEAE	treatment-emergent adverse event
TGF	transforming growth factor beta
T_{max}	time of occurrence of C_{max}
UACR	Urine Albumin to Creatinine Ratio
ULN	upper limit of normal
UPCR	Urine Protein to Creatinine Ratio
V_{ss}	apparent volume of distribution at steady state
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Duchenne Muscular Dystrophy

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

The progression of DMD follows a highly predictable course. Significant motor deficits may be present during the first year of life, but diagnosis is usually made between the ages of 3 to 5 years when toddlers begin to show functional symptoms (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).

Existing interventions for DMD patients with mutations amenable to exon skipping are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation. Current pharmacologic treatments, such as corticosteroids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function (Beenakker 2005; Biggar 2006; Pradhan 2006). However, their benefits are only temporary, and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, Cushingoid facies and habitus, and cataracts (Biggar 2006; Manzur 2004).

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

Ribonucleic acid (RNA) therapeutics are compounds composed of heterocyclic nucleobases (adenine, cytosine, guanine, and thymine, or analogues) linked together on an oligomer backbone that supports hybridization via Watson-Crick base pairing with specific complementary RNA targets. RNA therapeutics can be synthesized to bind targeted RNA sequences in a pathogen or pathogenic process to treat a wide range of diseases through positively or negatively modulating gene expression. A relatively new use of RNA therapeutics is to target a pre-messenger RNA (mRNA) in the nucleus of a cell to influence the splicing process that creates a mature mRNA. Referred to as “exon skipping,” this approach allows determination of which exons will be incorporated into the mature mRNA to be translated into the protein product.

Phosphorodiamidate morpholino oligomers (PMOs) are a class of synthetic molecules based on a redesign of the natural nucleic acid structure. Phosphorodiamidate morpholino oligomers are distinguished from natural nucleic acids and other oligonucleotide therapeutic platforms by the attachment of nucleobases to a 6-membered morpholine ring as opposed to the 5-membered ribose ring found in RNA and deoxyribonucleic acid (DNA). Moreover, the morpholine rings are linked through neutrally charged phosphorodiamidate moieties as opposed to negatively charged phosphodiester linkages in RNA and DNA. These differences were designed to increase stability and address safety issues seen with some earlier oligonucleotide backbone chemistries.

Phosphorodiamidate morpholino oligomers are capable of avid, sequence-specific binding in vivo to regulatory sites in pre-mRNA and thus alter the splicing of a pre-mRNA transcript, such as that of dystrophin, causing the skipping (omission) of specific exons in the final mRNA. Approximately 80% of boys with DMD have out-of-frame deletions that could be amenable to exon-skipping therapies (Aartsma-Rus 2009). Several PMOs are being evaluated by Sarepta for the potential treatment of DMD, as exon skipping may enable the production of an internally deleted, functional dystrophin protein.

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

5.3. Clinical Experience with Eteplirsen

As of 24 June 2019, the eteplirsen clinical development program consists of 7 completed studies (Studies 4658-33, 4658-28, 4658-us-201, 4658-us-202, 4658-203, 4658-301 and 4658-204) and 2 ongoing studies (Studies 4658-102/[redacted]) in patients with DMD who were amenable to Exon 51 skipping. In addition, 2 Phase 1 studies (Studies 4658-101 and 4658-103) have been completed and 1 Phase 1 study (Study 4658-104) is ongoing in volunteers who do not have DMD.

Seven completed studies (Studies 4658-28, 4658-us-201, 4658-us-202, 4658-203, 4658-101, 4658-301 and 4658-103) have contributed to the pharmacokinetic profile of eteplirsen. There was little or no accumulation in plasma following weekly administration. Maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased in an approximately dose-proportional or slightly less than proportional manner. Urinary elimination of the active ingredient without metabolites was the predominant route of excretion. Based on the results of Study 103, an increase in eteplirsen exposure was observed in non-DMD adults with mild to moderate renal impairment.

Clinical efficacy results that include ambulatory and pulmonary function have been evaluated in completed Studies 4658-us-201/202, 4658-203, 4658-204 as well as Study 4658-301. Study 4658-us-201/202 provides long-term results across multiple ambulatory and respiratory endpoints over the course of 4 years. Studies 4658-301 (interim analysis) and 4658-204 provide

additional supportive evidence of ambulatory and pulmonary function over the course of 2 years. Pooled results from these 3 studies (Studies 4658-us-201/202, 4658-203, and 4658-204) were compared with data from comparable external control cohorts and a comprehensive review of literature describing the natural history of DMD. Results from these analyses demonstrated a divergence, starting at Year 2, favoring eteplirsen-treated patients. Study 4658-301 confirmed mechanism of action showing increasing exon skipping leading to 0.52 % dystrophin levels by Western Blot which significantly & consistently increased over Baseline starting at Week 24 and continuing to Week 96 (n=77). Overall, the long-term safety profile of eteplirsen for treatment of patients with DMD was consistent with previous study data.
Study 4658-203 was a Phase 2, multicenter, open-label trial to evaluate the safety and tolerability of eteplirsen in patients aged 4 to 6 years with genotypically-confirmed DMD with genetic mutations amenable to treatment by exon 51 skipping. The study enrolled 26 patients who received once-weekly intravenous (IV) infusions of 30 mg/kg eteplirsen for up to 96 weeks. Treatment with eteplirsen was well tolerated and safety results were consistent with a favorable safety profile for eteplirsen. [redacted]

As of 24 June 2019, 182 patients with DMD and 59 non-DMD subjects have been treated with eteplirsen in clinical studies, including 175 who received IV eteplirsen and 155 who received 30 mg/kg or higher. Of the 182 patients, 17 and 135 patients received at least 48 and 96 weeks of eteplirsen treatment, respectively. This includes 12 patients from Study 201/202 who have been treated for over 5 years. These studies demonstrated that treatment with eteplirsen was generally well-tolerated at doses of 30 mg/kg (N=149) and 50 mg/kg (N=6) and there were no observed difference in safety between these 2 doses.

Based on the cumulative available safety data from these studies, eteplirsen has been shown to be well tolerated, with low rates of serious or severe adverse events (AEs).

Refer to the Investigator's Brochure for further details.

5.4. Rationale for the Current Study

The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of eteplirsen over at least 48 weeks of dosing, and up to 96 weeks of dosing, in male patients with DMD with a deletion mutation amenable to exon 51 skipping between 6 months to 48 months of age (inclusive). Eteplirsen has not previously been studied in this age group.

5.5. Benefit and Risk Assessment

Details about the known and expected benefits and risks of, and expected AEs associated with, eteplirsen treatment are provided in the eteplirsen Investigator's Brochure.

Eteplirsen has been granted accelerated approval in the United States (US) by the Food and Drug Administration. This was based on the observation of dystrophin production in some patients and the safety experience in patients with DMD participating in clinical trials, who were 4 years of age or older, which includes the age range specified for this study. Patients have also used commercially available eteplirsen since the approval in September 2016.

To date, eteplirsen has been well tolerated, with low rates of serious or severe AEs. No major safety risk has been identified in patients dosed with eteplirsen, including patients dosed with up to 50 mg/kg once weekly for more than 4 years.

Risks with eteplirsen include infusion-related reactions, hypersensitivity reactions, and potential renal toxicities including proteinuria or decreased renal function. These events have been seen in prior experience with eteplirsen with lower doses and are usually mild and resolve without clinical or pharmaceutical treatment. The use of higher doses of eteplirsen in this protocol could lead to more frequent or more severe reactions than seen with lower doses. Regularly scheduled review by a Safety Review Committee during the open-label period and a Data Monitoring Committee (DMC) during the double-blind period will look at aggregate unblinded data to determine the relative risk-benefit of continuing the dose or the study. Investigators are allowed to withhold dosing and must discuss such actions with the Medical Monitor. Further details on the safety of eteplirsen can be found in the Investigator's Brochure.

Based on the mechanism of action of eteplirsen and the benefit of eteplirsen treatment in DMD patients with mutations amenable to skipping exon 51, it is expected that patients in Study 4658-102 may derive a clinical benefit from treatment with a higher dose of eteplirsen.

Taken together, these considerations support that patients participating in Study 4658-102 will not be exposed to undue risk and may potentially experience some clinical benefit.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

- To evaluate the safety and tolerability of eteplirsen administered once weekly by IV infusion in male DMD patients ages 6 months to 48 months, inclusive.

6.2. Secondary Objective

- To determine the PK of eteplirsen at the 2-, 10-, 20-, and 30-mg/kg dose levels, administered once weekly by IV infusion in male DMD patients ages 6 months to 48 months, inclusive.

6.3. [redacted]

- [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, open-label, dose-escalation study to evaluate the safety, tolerability, PK, and efficacy of once-weekly IV infusions of eteplirsen in approximately 12 male patients, ages 6 months to 48 months (inclusive), who have genotypically confirmed DMD with a deletion mutation amenable to exon 51 skipping.

Patients will be evaluated for inclusion during the Screening Period of up to 2 weeks to assess eligibility. 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, patients will undergo screening assessments as indicated in Table 2 (Schedule of Events).
- Blood samples for the screening clinical safety laboratory assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1.

Patients will be enrolled into 1 of 2 age cohorts, as presented in Table 4.

Table 4: Study Cohorts and Enrollment Criteria

Cohort	Age	Criteria for Enrollment
1: approximately 6 patients	24 to 48 months old	Meet all screening and I/E criteria.
2: approximately 6 patients	6 to <24 months old	DMC approves initiation of cohort Meet all screening and I/E criteria.

Abbreviations: I/E = inclusion/exclusion.

After the first 3 patients in Cohort 1 have completed 12 weeks of eteplirsen therapy (ie, 12 infusions, including 2 infusions each at 2, 4, 10, and 20 mg/kg, and 4 infusions at 30 mg/kg), the DMC will review the safety data and determine whether to begin enrollment of the younger patients (Cohort 2).

A DMC will review safety data at least weekly through the first 12 weeks of dosing for the first 3 patients of each age cohort. Reviews will be at least quarterly thereafter.

The dose-titration period will last 10 weeks overall (1 infusion/week) to slowly achieve the target dose of 30 mg/kg. Eteplirsen dosing will begin at 2 mg/kg for 2 weeks (Weeks 1 and 2) and will escalate to 4 mg/kg (Weeks 3 and 4), 10 mg/kg (Weeks 5 and 6), 20 mg/kg (Weeks 7 and 8), and 30 mg/kg (Weeks 9 and 10). Patients will continue to receive 30 mg/kg eteplirsen for the duration of the study. The duration of each patient's treatment in the study is expected to be at least 48 weeks (including the 10-week titration period), and patients may continue to receive treatment in the study for up to 96 weeks determined by the Investigator based on the absence of any safety signal and an indication of clinical benefit. [redacted]

[redacted]

In addition, study drug may be interrupted or discontinued for specific safety reasons.

Safety will be regularly assessed throughout the study via the collection of AEs, clinical safety laboratory tests (blood chemistry, hematology, renal function, coagulation, and urinalysis), electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations.

Plasma and urine samples for PK assessments will be collected at Week 2 (2-mg/kg dose level), Week 6 (10-mg/kg dose level), Week 8 (20-mg/kg dose level), and at Weeks 10 and 24 (30-mg/kg dose level). Serial PK samples will be collected pre-dose, immediately prior to the end of infusion (prior to flush), and approximately 1-3 hours and 6-8 hours after completion of study drug infusion. Urine PK samples will be collected over the first 4 hours after start of infusion.

[redacted]

Approximately 4 weeks after the last eteplirsen infusion (regardless of the duration of the patient's participation in the study), patients will be required to return to the study site for safety evaluations. The total duration of patient participation, including Screening, Titration/Treatment, and Safety Follow-up periods is up to 101 weeks.

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

7.2. Dose Selection Rationale

As this is the first safety and tolerability study to be conducted in pediatric patients' ages 6 months through 48 months (inclusive), eteplirsen will be dosed weekly in a dose-titration fashion starting at 2 mg/kg to slowly achieve the target dose of 30 mg/kg over the course of 10 weeks.

The selection of a 2-mg/kg starting dose for this study is based on nonclinical data as well as clinical safety experience with eteplirsen. Based on mean maximum plasma concentration (C_{max}; 4.82 µg/mL) and area under the concentration-time curve from time 0 to 24 hours postdose ($AUC_{0\text{-}24hr}$; 6.20 µg•hr/mL) determined at the 2.0-mg/kg dose level in Study 4658-28, safety margins to the no-observed-adverse effect levels in juvenile rats (300 mg/kg) and non-human primates (320 mg/kg) are expected to be at least 50× the 2.0-mg/kg starting dose proposed for Study 4658-102.

Dose selection for the group aged 6 months to 4 years old is based on the assumption that efficacy relates to exposure, defined by the use of AUC. The 30-mg/kg dose was chosen as the target dose based on results from the Phase 2, double-blind, placebo-controlled, multiple-dose study, Study 4658-us-201, and its open-label extension, Study 4658-us-202. As described in Section 5.3, these studies assessed the efficacy, safety, tolerability, and PK of 2 eteplirsen doses (50 mg/kg and 30 mg/kg) administered as IV infusions in twelve 7- to 13-year-old pediatric patients diagnosed with DMD with a deletion mutation amenable to exon 51 skipping. 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 doses from Week 1 (52% and 42% of normal, respectively, or 47% for the combined groups; data on file). 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, 30-mg/kg dose was selected as the more conservative choice, because patients presumably would receive this drug as a life-long treatment. To date, there is no evidence that the response differs across age groups.

At the time that this trial was designed, 150 patients have been dosed with eteplirsen, 124 of which received 30 or 50 mg/kg and 81 patients have been dosed for at least 1 year. The overall review of safety data for these 150 patients has not identify any significant safety concerns with eteplirsen. Further safety review was conducted in 26 patients who were 4 to 6 years of age and enrolled in Study 203. Overall, the safety data in Study 203 is consistent with the overall safety profile of eteplirsen with low rates of serious (11.5%) and severe (3.8%) AEs. Therefore, given the safety experience with eteplirsen to date, it is considered appropriate to increase the starting dose from 0.5 mg/kg, which was used in Study 28, to the 2 mg/kg proposed for Study 4658-102.

As of 24 June 2019, 182 patients with DMD and 59 non-DMD subjects have been treated with eteplirsen in clinical studies, including 175 who received IV eteplirsen and 155 who received 30 mg/kg or higher. Of the 182 patients, 17 and 135 patients received at least 48 and 96 weeks of eteplirsen treatment, respectively. This includes 12 patients from Study 201/202 who have been treated for over 5 years. These studies demonstrated that treatment with eteplirsen was generally well-tolerated at doses of 30 mg/kg (N=149) and 50 mg/kg (N=6) and there were no observed difference in safety between these 2 doses.

7.3. Study Endpoints

7.3.1. Primary Endpoint

The primary endpoint is safety and tolerability of eteplirsen in this study population, as measured by:

- Incidence of AEs
- Abnormal changes from Baseline or clinically significant worsening of clinical safety laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Abnormal changes from Baseline or worsening of vital signs
- Abnormal changes from Baseline or worsening of physical examination findings
- Abnormal changes from Baseline or clinically significant worsening of ECGs and ECHOs

7.3.2. Secondary Endpoint

The secondary endpoint is to determine the PK of eteplirsen by population PK methods, including assessment of the following PK parameters (if evaluable):

- C_{max}

- Time of C_{max} (T_{max})
- AUC
- Apparent volume of distribution at steady state (V_{ss})
- Clearance (CL)
- Elimination half-life (t½)
- Amount of drug eliminated in urine (Ae%)

7.3.3. [redacted]

CCI [redacted]

7.4. Discussion of Study Design

DMD is a rare, serious, debilitating, and ultimately fatal, disease for which there is an urgent need to develop safe and effective therapies. In order to efficiently meet this urgency and the needs of the patient community, the study is open label with no placebo control.

[redacted]

No other disease-modifying treatment exists to serve as an appropriate active comparator for this patient population of boys aged 6 to 48 months; ataluren is commercially available in the European Union, but is not indicated for use in patients with exon 51 amenable mutations (PTC Therapeutics).

The patients in this study will have an established clinical diagnosis of DMD with a deletion mutation amenable to exon 51 skipping. These are the patients for whom eteplirsen is potentially effective and may result in slowing their disease progression. The age range for the patients in this study (6 to 48 months old, inclusive) was chosen in order to establish the safety profile of eteplirsen in this age group to provide data to support the safety of early intervention.

To protect patient safety, gradual dose titration of eteplirsen will occur over the first 10 weeks, followed by once-weekly infusion of the target dose of 30 mg/kg, with weekly reviews of study data by the DMC through the first 12 weeks of dosing for the first 3 patients of each age cohort,

and at least quarterly thereafter. In addition, study drug may be interrupted or discontinued for specific safety reasons.

Patients will continue to receive once-weekly infusions for at least 48 weeks and up to 96 weeks to obtain safety data in this population. Refer to the Investigator's Brochure for information on the safety of eteplirsen.

Because DMD is a rare disease, the accrual of patients for enrollment may be challenging. To allow for efficient recruitment of the appropriate patient population, this study is being conducted at multiple sites. The selected sites for this study are centers of excellence for treatment of DMD, have extensive experience collaborating on clinical trials, and are therefore optimally suited to enroll and conduct the present study.

7.5. Data Monitoring Committee

The DMC will be comprised of a group of individuals with pertinent methodological and clinical expertise relevant to the study design and background population, that review the conduct of the study and the emerging safety, PK, and efficacy data on an ongoing basis in order to ensure that clinical trial participants are not exposed to unreasonable or unnecessary risks. The DMC will advise the study team and study investigators on safety aspects of dose interruption/continuation and dose escalation for the study. DMC membership will begin before the start of the clinical trial and continue for its duration.

The activities and composition of this committee will be outlined in the DMC Charter, which will be ratified during the initial DMC meeting, prior to the commencement of dosing of the study patients. The reviews will be performed at least weekly through the first 12 weeks of dosing for the first 3 patients of each age cohort and at least quarterly thereafter. Oversight and monitoring of the clinical study by the DMC will be performed in compliance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. These safety monitoring functions are distinct from the requirements for study review and approval by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Patients

Approximately 12 patients will be enrolled in this study.

8.2. Patient Inclusion Criteria

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

- Be a male between 6 months to 48 months of age, inclusive.
- Have an established clinical diagnosis of DMD with a deletion mutation amenable to exon 51 skipping (eg, deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63).
- Have a parent(s) or legal guardian(s) who is able to understand and comply with the study requirements and is willing to provide written informed consent for the patient to participate in the study.

8.3. Patient Exclusion Criteria

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

- Has received any pharmacologic treatment that might have an effect on muscle strength or function within 12 weeks prior to dosing at Week 1 (eg, growth hormone, anabolic steroids).
- Has received previous or current treatment with any experimental treatment. Prior drisapersen therapy is permitted if a patient has not received drisapersen for 6 months prior to the Week 1 dose.
- Has a clinically significant illness other than DMD, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease, or malignancy likely to impair the patient's ability to participate in this study.
- Has a clinically significant laboratory abnormality that is either not expected or is of a greater severity than what is expected in DMD patients.
- Has any other condition that, in the Investigator’s opinion, could interfere with the patient’s participation in the study.

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

Patients are considered completers for the purpose of analysis once the Week 48 assessments have been completed. Patients may continue in the study up to and including 96 weeks based on the judgement of the Investigator (described further in Section 7.1); however, a Safety Follow-up visit will occur approximately 4 weeks after the last dose administered regardless of the patient’s duration 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 Safety Follow-up visit (approximately 4 weeks after the last dose is administered).

8.5. Completion of the Trial

The trial will be considered to have been completed upon the last visit of the last patient who had their treatment extended to Week 98.

8.6. Patient Withdrawal Criteria

Any patient can decide to withdraw from study participation at any time for any reason. A patient who discontinues may be replaced at the discretion of the Sponsor. In addition, the study Sponsor may decide to stop the study participation of any patient as deemed necessary. The Investigator may also stop the study participation of any patient at any time. Reasons for withdrawal from the study 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 without the prior written authorization of the Sponsor.

The Investigator or study staff will document the reason(s) for treatment discontinuation.

Patients who have received at least 1 dose of study treatment and who are withdrawn from treatment within 28 days after a functional assessment visit will be asked to return for an Early Termination visit (to complete the Week 96 assessments) approximately 28 days after their last dose. Patients who receive at least 1 dose of study treatment who are withdrawn from treatment more than 28 days after a functional assessment visit will be asked to complete all early termination (Week 96) assessments within approximately 28 days after the last dose.

Patients withdrawn from treatment will not be replaced.

8.7. Study Discontinuation

If the Sponsor, the Investigator, the Medical Monitor, the study monitor, 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, the IRB/IEC, and the Medical Monitor.

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

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate

- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements consistent with the European Clinical Trial Directive 2001/20/EC

9. TREATMENT OF PATIENTS

9.1. Investigational Product

Eteplirsen drug product is supplied as a sterile, phosphate-buffered saline solution in single-use, 2-mL vials each containing 2 mL of eteplirsen at 50 mg/mL. The solution is a clear to slightly opalescent and colorless liquid that may contain white to off white particles. Eteplirsen will be administered once a week by IV infusion.

9.1.1. Packaging and Labeling

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

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

9.1.2. Storage

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

9.2. Treatments Administered

Eligible patients will receive a once weekly IV infusion of eteplirsen for up to 96 weeks. Eteplirsen should be prepared for dosing by following the steps detailed in the study-specific Pharmacy Manual.

The starting dose is 2 mg/kg eteplirsen, with escalation to 4, 10, 20, and 30 mg/kg over the course of the dose-titration period.

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

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

The administered dose is calculated by patient weight, which will be collected on a weekly basis and used to calculate the dose to be administered at the next visit(s). For example, the weight collected at Week 2 will be used to calculate the doses to be infused during the Week 3 visit.

Eteplirsen should be diluted in a normal saline, where the final volume, after eteplirsen has been added, equals the volume appropriate for the patient's weight. The drug delivery bag, syringe or flask is to be labeled in accordance with standard pharmacy practice and to include total volume as well as drug dose in milligrams. Eteplirsen will be diluted in normal saline to a total volume per Table 5 and infused IV for approximately 35 to 60 minutes using an infusion or syringe

pump. It is recommended that a topical anesthetic cream be applied to the infusion site prior to each administration of eteplirsen.

Table 5: Example Eteplirsen Dilution Scheme

Patient Weight	Total Eteplirsen Dose (30 mg/kg)	Total Volume of Eteplirsen Drug Product	Dilution in Saline up to Total Volume of:	Maximum Eteplirsen Concentration in Infusion
<5 kg	<150 mg	<3 mL	10 mL	15 mg/mL
5 to 10 kg	150 to 300 mg	3 to 6 mL	15 mL	20 mg/mL
10 to 15 kg	300 to 450 mg	6 to 9 mL	25 mL	18 mg/mL
15 to 25 kg	450 to 750 mg	9 to 15 mL	50 mL	15 mg/mL
>25 kg	>750 mg	>15 mL	100 mL	

Note: Refer to the Pharmacy Manual for other dosing dilution schemes.

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. Patients are permitted to continue a chronic, stable regimen of corticosteroids; however, the corticosteroid should not be administered during the infusion of eteplirsen.

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

9.2.1. Dose Modification, Reduction, or Delay

9.2.1.1. Dose Interruption

The following rules apply to individual dosing interruption, ie, the criteria for dosing interruption of 1 patient. Further administration of eteplirsen must be discontinued if any of the following occur:

- Any serious adverse event (SAE) considered to be related to eteplirsen, unless the SAE is deemed related to the underlying disease
- See Section Section 10.3.4 for Safety Monitoring, Additional Investigations and Stopping Rules

If a patient meets one of the above criteria or under Section 10.3.4, the study monitor should be immediately notified, and dosing should be suspended until the patient's safety information can be reviewed by the DMC. Dosing may resume only after approval of the DMC, Sponsor, and Investigator, and after approval of a substantial amendment by the competent authority.

Conditions that may warrant interrupting dosing for all patients in the study for additional safety review include, but are not limited to:

- Any SAE of life-threatening or fatal outcome assessed as related by the Investigator
- > 2 patients with severe AEs that result in interruption of individual patient dosing (described earlier in Section 10.3.4)
- Any unexplained or drug-related organ failure (eg, liver or renal failure)

The DMC will monitor safety data on an ongoing basis. If the DMC determines that the criteria for study interruption are met, dosing will be suspended until all available patient information related to the event of interest can be reviewed in more detail. Discontinuation of dosing for an individual patient may occur based on the recommendation of the DMC, investigator, the patient, and the local Independent Ethics Committee (IRB/IEC).

[redacted]

Stopping rules are provided in Section 8.6 (Patient Withdrawal Criteria) and Section 8.7 (Study Discontinuation).

9.2.1.2. Dose Escalation

Increases in dosing up to 30 mg/kg are described in Section 9.2.

9.3. Randomization and Blinding

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

9.4. Prior and Concomitant Medications

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

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

- Previous or current investigational agents (with the exception of drisapersen: patients may be included in the study if they have not received drisapersen for 6 months prior to the Week 1 dose)
- Immunosuppressants (other than oral or systemic corticosteroids; the corticosteroid should not be administered during the infusion of eteplirsen)
- Previous (within 12 weeks prior to the Week 1 dose) or current systemic aminoglycoside antibiotic or statin

In general, drug therapies that are not excluded per the entry criteria, including over-the-counter medications, may be used before enrollment and throughout the study. However, the number of over-the-counter medications should be limited and the dosage of any medication should be constant for at least 1 month prior to starting study treatment and throughout the study, especially during the dose-escalation period and throughout the first 6 months in the study, unless clinically indicated.

The Investigator should contact the Medical Monitor if he/she is unsure about changing a specific medication.

9.5. Treatment Compliance

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

10. STUDY ASSESSMENTS

10.1. Study Schedule of Events

A detailed schedule of the study assessments and time points is shown in Table 2 and Table 3.

10.2. Screening/Baseline Assessments

10.2.1. Informed Consent

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

10.2.2. Demographics and Medical History

Demographic information (eg, age, race, ethnicity, body weight, height, body mass index) and medical history (including treatment history) will be obtained for all patients.

10.2.3. Genotyping

10.2.3.1. DMD

A blood sample will be obtained to determine DMD genotype (or confirm if previously tested). Patients not previously genotyped may be consented and have genotype performed as part of the study. The blood sample for genotyping can be drawn at the Screening visit or any time prior to the Week 2 visit so that total blood volume taken for the Screening visit does not exceed recommendations (Section 17.1). Patients may start dosing based on historical genotyping results, provided that these results fulfill the required criteria described in Inclusion Criterion #2 (Section 8.2); however, all patients must undergo genetic testing to confirm the deletion mutation amenable to exon 51 skipping. Patients whose genotype is not confirmed to be amenable to exon 51 skipping will be withdrawn from the study.

10.2.3.2. LTBP4 and SPP-1

A blood sample will be obtained for latent transforming growth factor beta (TGF) binding protein 4 (LTBP4) and secreted phosphoprotein 1 (SPP-1) genotype for sensitivity analysis. The blood sample for single-nucleotide polymorphism analysis can be drawn at the Screening visit or any time during the dose-titration period, such that total blood volume taken at any given visit does not exceed recommendations (Section 17.1).

10.2.4. Other Assessments

Screening will also include clinical safety laboratory assessments, vital signs, physical examination, height/length and weight, a 12-lead ECG, an ECHO, assessment of previous and current medications/therapies, assessment of pre-treatment AEs, [redacted]

10.3. Safety Assessments

10.3.1. Physical Examination

The Investigator or a medically qualified Subinvestigator will perform physical examinations at designated study visits, including examination of general appearance; head, ears, eyes, nose, and throat (HEENT); heart; lungs; chest; abdomen; skin; lymph nodes; musculoskeletal; and neurological systems.

10.3.2. Vital Signs

Vital signs (blood pressure, heart rate, respiration, and temperature) will be measured at the time points specified in Table 2 and Table 3. Refer to the Study Operations Manual for more details on the methods for obtaining vital signs.

For infusion visits, vital signs are to be collected within 60 minutes prior to infusion and within 5 (±2)after the end of infusion, and at 30 (±5), and 60 minutes (±10) after the end of the infusion. If the patient has not experienced an infusion reaction after the first 48 weeks of treatment, vital sign assessments may be limited to approximately 30 minutes prior to infusion and approximately 30 minutes after the end of the infusion. All assessments will be performed after patients have remained calm for 5 minutes. Pulse rate and respiratory rate should be measured over 1 minute.

10.3.3. Height/Length and Weight

Height/length and weight will be measured at the time points specified in Table 2 and Table 3 prior to study drug infusions, to determine the volume of study drug to be administered. Details about how weight measurements are obtained are provided in the Study Operations Manual. If a patient's weight or height/length varies by more than 10% from the prior visit, the patient should be re-weighed to confirm the result, and an explanation of the change should be documented.

10.3.4. Safety Monitoring, Additional Investigations and Stopping Rules

10.3.4.1. Safety Monitoring for Liver Chemistry Tests

Liver chemistry tests need to be monitored as specified in the Schedule of Events (Table 2).

Initial abnormal liver chemistry test result(s) needs to be confirmed if:

- Gamma-glutamyl transferase (GGT) or glutamate dehydrogenase (GLDH) or Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) measurement is > 3 x the upper limit of normal (ULN) (or > 2 x Baseline value if the Baseline value was > ULN) at any time during the study.

Patients with confirmed liver chemistry test results (as above) need to have their liver chemistry tests (GGT, GLDH, ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.

Additional Investigations:

Patients with confirmed abnormal liver chemistry test results (as above) are recommended to have the following evaluations performed:

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; Non-Alcoholic SteatoHepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography (CT) or magnetic resonance imaging (MRI) scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.

Stopping Rules for Liver Test Results:

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

- GGT or GLDH > 8 x ULN, which is confirmed
- GGT or GLDH > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
- GGT or GLDH > 3 x ULN, which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
- GGT or GLDH > 3 x ULN which is confirmed, and the new appearance (ie, onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%) felt by the Investigator to be potentially related to hepatic inflammation.

10.3.4.2. Safety Monitoring for Renal Function

Renal tests need to be monitored as specified in the Schedule of Events (Table 2). Patients with the following test results need to undergo repeat testing for confirmation of abnormal test results:

- Protein ≥ 2+ (dipstick)
- Urine Protein to Creatinine Ratio (UPCR) ≥ 150mg/g
- Urine Albumin to Creatinine Ratio (UACR) ≥ 30mg/g
- Serum Creatinine ≥ 0.3 mg/dL above baseline

- Serum Creatinine ≥ 1.5x ULN
- Estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m2
- Red blood cells (RBCs) > 1/hpf
- Elevated Cystatin C > ULN
- Elevated kidney injury molecule 1(KIM-1) > ULN

Additional Investigations:

24- hour urine collection needs to be undertaken to quantify any proteinuria and glomerular filtration rate (GFR) changes indicated by confirmed results as above. Additional evaluations including nephrology consultation, renal US/CT/MRI, renal biopsy, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

Stopping Rules for Renal Test Results:

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will be stopped permanently:

- Quantitative total urine protein measurement of ≥ 1 g/24 hours
- Measured GFR (creatinine clearance) ≤ 45 mL/min/1.73m^2
- Gross hematuria
- Any RBC Casts
- Persistent microscopic hematuria ≥ 3 RBCs/hpf for 3 consecutive weeks

Safety Monitoring for Hypersensitivity

Patients will be monitored for occurrence of allergic reactions primarily via monitoring adverse events as specified in the Schedule of Events (Table 2). Patients will be instructed to promptly report any signs or symptoms of fever or constitutional symptoms that may arise during the study and the Investigator needs to closely evaluate all potential causes, including concomitant illness.

Additional Investigations:

Patients who experience significant or persistent constitutional symptoms need to be discussed with the Sponsor Medical Monitor to determine whether additional monitoring or laboratory tests are required. Additional evaluations including immunology consultation, tests for allergic reactions (absolute eosinophils, serum/plasma tryptase), may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

Stopping Rules for Hypersensitivity AEs:

In the event of a confirmed hypersensitivity AE meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will have their treatment permanently discontinued.

- Anaphylaxis, anaphylactoid reaction, or angioedema
- Any serious allergic reaction

Safety Monitoring for Platelet Count Results

The platelet count needs to be monitored as specified in the Schedule of Events (Table 2).

Patients who have a confirmed occurrence of platelets < 75,000/ mm^3 need to have the following evaluations performed:

- Complete blood count (CBC) with reticulocytes
  - Peripheral blood smear
  - Coagulation panel (prothrombin time /INR, activated partial thromboplastin time)
  - High-sensitivity C-reactive protein

Additional Investigations:

Additional platelet evaluations for confirmed, unexplained significant platelet count reductions, including hematology consultation, fibrinogen, fibrinogen split products/D-dimer, von Willebrand factor, total immunoglobulins, complement levels, viral serologies, auto-antibody screen, antiplatelet antibodies and anti-PF4 assay, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

Stopping Rules for Platelet Test Results:

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will be stopped permanently:

- Platelet count < 50,000/mm^3

Safety Monitoring for Rhabdomyolysis

Rhabdomyolysis must be monitored by urine dipstick and adverse events as specified in the Schedule of Events (Table 2).

Patients who have confirmed heme+ dipstick urinalysis need to be evaluated for urine microscopy and the following AEs:

- Rhabdomyolysis

- Acute onset or exacerbation of Myalgia
- Myoglobinuria
- Chromaturia (eg, tea-colored urine)

Additional Investigations:

In case of any of the adverse events above, subjects need to have evaluations of myoglobinuria, creatine kinase (CK), renal function (eg, serum cystatin C) and serum chemistry two or three times weekly until values reach usual/pre-event levels or stabilize.

In addition, investigators should obtain a more detailed history of symptoms, preceding activity and hydration status, concomitant drug use, and recent or concurrent infections. Additional evaluations, including rheumatology/immunology consultations and anti-muscle antibodies, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

10.3.5. Clinical Safety Laboratory Evaluations

The following routine clinical safety laboratory tests will be collected at the time points specified in Table 2 and Table 3, will be analyzed by an accredited central laboratory selected by the Sponsor, and will be 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, ALP, amylase, ALT, AST, GGT, GLDH, C-reactive protein (CRP), CK, and serum cystatin C
Hematology:	CBC with differential
Coagulation Screen:	Prothrombin time, International Normalized Ratio, and activated partial thromboplastin time
Routine Renal Monitoring	• Quantitative urinalysis: total protein to creatinine ratio (UPCR), urine albumin-to-creatinine ratio (UACR), kidney injury molecule 1 (KIM-1), and urinalysis (pH, specific gravity, protein, glucose, ketones, cytology, hemoglobin • Renal function blood tests: creatinine, blood urea nitrogen, and cystatin C • Urine dipstick testing

Persistent, unexplained abnormalities on routine renal blood test monitoring will result in additional renal function tests such as eGFR and 24 hour urine testing for protein.

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 or not. 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 are assessed to be not related to the administration of IP or other protocol-specific procedures, and additional assessments are not medically indicated.

10.3.5.1. Laboratory Assessments of Interest

The review of the DMC will include evaluation of laboratory assessments of interest, which include:

- Any ≥Grade 2 (moderate) or serious event without an alternative etiology that the Investigator deems is related to study drug
- Two consecutive drug-related serum creatinine levels ≥2 × ULN without an alternative etiology.
- CK levels >50,000 U/L
- A confirmed, unexplained, increase in GGT or GLDH >3 × ULN and either an increase in bilirubin >2 × ULN or nascent prothrombin time >2 × ULN concurrently, without an alternative etiology

10.3.6. Electrocardiogram

Twelve-lead ECGs will be obtained at the time points specified in Table 2 and Table 3. ECGs will be performed at a consistent time of day throughout the study, [redacted] but before performing any invasive procedures (ie, blood sampling or study drug infusions). ECGs should be performed by trained staff after the patient is in the supine position, resting, and quiet, when possible. 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.

Clinical significance is defined as any variation in ECG findings that has medical relevance resulting in an alteration in medical care. If clinically significant worsening from baseline is noted, the Investigator will continue to monitor the patient with additional assessments until:

- Findings have returned to normal and/or baseline levels; or
- In the judgment of the Investigator together with the Sponsor's Medical Monitor, abnormal findings are assessed to be not related to the administration of IP or other protocol-specific procedures, and additional assessments are not medically indicated.

10.3.7. Echocardiogram

A standard 2 dimensional ECHO will be obtained at the time points specified in Table 2 and Table 3. ECHOs will be performed at a consistent time of day throughout the study, and will be

performed [redacted] but before performing any invasive procedures (ie, blood sampling or study drug infusions). The ECHO will be obtained, reviewed, and interpreted by medically qualified personnel using a central vendor according to pre-specified criteria. Left ventricular ejection fraction (LVEF) will be noted. The Investigator will review the results of the ECHO report and determine if the findings are clinically significant.

Clinical significance is defined as any variation in ECHO findings that has medical relevance resulting in an alteration in medical care. If clinically significant worsening from baseline is noted, the Investigator will continue to monitor the patient with additional assessments until:

- Findings have returned to normal and/or baseline levels; or
- In the judgment of the Investigator together with the Sponsor's Medical Monitor, abnormal findings are assessed to be not related to the administration of IP or other protocol-specific procedures, and additional assessments are not medically indicated.

10.3.8. 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/legal guardian signs informed consent. Information on any physiotherapeutic intervention must be collected in detail for this study. See Section 9.4 for details on permitted concomitant medications.

10.3.9. Adverse Events

AEs will be monitored throughout the study, from signing of the informed consent through each patient's safety follow-up visit, which will occur approximately 4 weeks after the last infusion regardless of the patient's duration in the study.

10.4. Pharmacokinetic Assessments

10.4.1. Blood Sample Collection

Serial plasma PK sampling will be performed on all patients at the visits specified in Table 2. Serial PK samples will be collected from the contralateral arm collected pre-dose, immediately prior to the end of infusion (prior to flush) and approximately 1 -3 hours and 6-8 hours after completion of study drug infusion.

Refer to the Study Laboratory Manual for additional details on handling and processing PK samples.

10.4.2. Urine Sample Collection

Urine PK samples will be collected over the first 4 hours after start of infusion at the visits specified in Table 2. Refer to the Study Laboratory Manual for details on handling and processing urine samples.

10.5. [redacted]

[redacted]

10.5.1. [redacted]

[redacted]

10.5.2. [redacted]

[redacted]

10.5.3. [redacted]

[redacted]

[redacted]

10.5.4. [redacted]

[redacted]

11. ADVERSE EVENTS

11.1. Collection of Adverse Events

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

All AEs from the time of informed consent through the safety follow-up visit (which will occur approximately 4 weeks after the last infusion regardless of the patient's duration in the study) will be recorded in each individual patient's electronic case report form (eCRF). If at any time after the patient has completed participation in the study, the Investigator or study staff becomes aware of a SAE that the Investigator believes is related to the IP (Section 11.3.1) or is related to a study procedure (Section 11.3.2), then the event and any known details must be reported promptly to the Sponsor.

11.2. Definition of Adverse Events

11.2.1. Adverse Event

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

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

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

11.2.2. Serious Adverse Event

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.

11.3. Classification of Adverse Events

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

11.3.1. Relationship to Investigational Product

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

Unrelated:	There is no reasonable possibility that the event is related to the investigational drug product.
Possibly/Probably Related:	The event could possibility be related/is likely related to the investigational drug product.
Related:	There is a reasonable possibility that the event is related to the investigational drug product.

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

11.3.2. Relationship to Study Procedures

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

Unrelated:	There is no reasonable possibility that the event is related to the study procedures.
Possibly/Probably Related:	The event could possibility be related/is likely related to the study procedures.
Related:	There is a reasonable possibility that the event is related to the study procedures.

11.3.3. Relationship to Underlying Disease

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

Unrelated:	There is no reasonable possibility that the event is related to the underlying disease.
Possibly/Probably Related:	The event could possibility be related/is likely related to the underlying disease.
Related:	There is a reasonable possibility that the event is related to the underlying disease.

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

11.3.4. Severity of Adverse Events

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

The Investigator will assess the severity of all AEs as mild, moderate, or severe, based on the following definitions:

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

11.3.5. Outcome

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

11.3.6. Action Taken Regarding the Investigational Drug Product

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

11.3.7. Expectedness of an Adverse Event

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

11.3.8. Suspected Unexpected Serious Adverse Reactions

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 the IRBs/IECs per the requirements of the concerned competent bodies. SUSARs will also be reported to study investigators.

11.3.9. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs (serious or nonserious) that are of special scientific and/or medical interest, for which ongoing and rapid communication by the Investigator to the sponsor is appropriate.

AESIs for this study are listed below. All AESIs should be reported as AEs to the sponsor within 24 hours of awareness irrespective of adverse event seriousness. This includes the events below that are based on lab abnormalities, which should be translated to an appropriate adverse even t term at the time of reporting.

Nephrotoxicity

- Proteinuria > 500 mg/24 hr
- eGFR <60 ml/min/1.73 m^2

Hepatotoxicity

- GGT or GLDH > 8 × ULN
- GGT or GLDH > 5 × ULN for more than 2 weeks
- GGT or GLDH > 3 × ULN and (total bilirubin >2 × ULN or international normalized ratio > 1.5)
- GGT or GLDH > 3 × ULN with the appearance of the following signs or symptoms: fatigue, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Hypersensitivity

- Anaphylaxis, anaphylactoid reaction, or angioedema
- Any severe allergic reaction
- Any severe complement mediated, inflammation event (eg, acute kidney injury, arteritis, myocarditis, pneumonitis)

Thrombocytopenia

- Platelet count < 75,000/mm^3

Infusion-related reactions

- All infusion related reactions considered severe (see Section 11.3.4), occurring within 24 hours of the eteplirsen infusion, should be reported to the Sponsor within 24 hours of awareness.

Infusion-related reactions may include headache, vomiting, diarrhoea, pyrexia, abdominal pain, upper, flushing and nausea. There may be pain at the site of the infusion as well as bruising surrounding the infusion site. Infections are also possible at the site of the infusion. All reactions grade 3 or higher, occurring within 24 hours of the eteplirsen infusion, should be reported to the Sponsor within 24 hours of awareness. Infusion-related reactions considered severe should be

reported to the Sponsor within 24 hours.

Rhabdomyolysis
Rhabdomyolysis adverse events of any severity.

11.4. 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 eCRF. Information to be recorded should include: a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to IP or study procedure or underlying disease; and any action taken will be recorded. Resolution occurs when the patient has returned to his baseline state of health or further improvement or worsening of the event is not expected.

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

11.5. Reporting Adverse Events

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

11.6. Special Situations

11.6.1. Overdose

An overdose is defined as administration of a dose that is >10% higher than the assigned dose per the protocol. 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 on the appropriate form and sent to the Sponsor or designee within 24 hours.

11.6.2. Pregnancy

If the female partner of a treated male subject becomes pregnant, the male subject must notify the Investigator within 24 hours of learning of the pregnancy. The Investigator must make every effort to ensure that the pregnant female is aware of the need to notify her healthcare provider regarding her male partner's participation in this clinical trial and his potential exposure to IP. The study site must complete a pregnancy form and send to the Sponsor or designee within 24

hours of learning of the pregnancy. The study site will make every effort to follow the pregnancy till outcome is known.

11.6.3. Medication Error

Medication Error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm, while the study drug is in the control of the health care professional, or in certain cases, the patient. Such incident may be due to health care professional practice, product labeling, packaging, and preparation, procedures for administration, and systems, including the following: prescribing, order communication, dispensing, nomenclature, compounding, distribution, administration, education, monitoring, and use. A medication error will be recorded on the appropriate form and sent to the Sponsor or designee within 24 hours.

11.6.4. Accidental/Occupational Exposure

Accidental/Occupational Exposure is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (eg, study drug given to wrong patient). An accidental/occupational exposure will be recorded on the appropriate form and sent to the Sponsor or designee within 24 hours.

11.6.5. Death

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

11.6.6. Responsibilities of the Investigator

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

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

11.6.7. 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
- Safety monitoring and recording of AEs
- AE processing and submission of expedited serious, unexpected, and related AEs to regulatory authorities per regulatory requirements
- Notification of expedited SAEs to sites
- Annual safety reporting to regulatory authorities and IRBs/IECs according to regional requirements

12. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

12.1. Recording of Data

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

12.2. Quality Assurance

The eCRFs 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 eCRF and for the Investigator or study coordinator to resolve. All changes to the eCRFs 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, eCRFs, 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.

12.3. Retention of Study Documents

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

However, these documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed upon designee.

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

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

13. STATISTICS

13.1. General Considerations

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

Revisions during the study may be made to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. 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 fo r missing data will be performed. Percentages of patients with AEs or laboratory abnormalities will be based on non-missing values.

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

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

The primary analysis will be done using the Week 48 data. In addition, all data through the end of study will also be analyzed.

13.2. [redacted]

[redacted]

13.3. Analysis Sets

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

13.4. Protocol Deviations

Protocol deviations will be listed. 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 deviation, use of prohibited therapies, etc.).

13.5. Disposition, Demographics, and Baseline Characteristics

The number and percentage of patients completing the study through Week 48 (ie, completers) or prematurely discontinuing before Week 48 will be summarized. Disposition will also be summarized over the entire 96-week duration of the study. Reasons for premature discontinuation will also be summarized.

Demographic characteristics including age (years), race, ethnicity, and baseline characteristics including height/length (cm), and weight (kg) will be summarized by age cohort and overall. Demographic data and baseline characteristics will be presented in data listings.

13.6. Medical History

Medical history will be presented in data listings.

13.7. Dosing and Compliance

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

13.8. Safety Analysis

13.8.1. Safety Variables

The safety variables are:

- Incidence of AEs
- Abnormal changes in clinical safety laboratory parameters
- Abnormal changes in vital signs
- Abnormal changes in physical examination findings
- Abnormal changes in ECG and/or ECHO parameters

13.8.2. Safety Analyses

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

13.8.2.1. Adverse Events

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

Multiple occurrences of the same AE (at the preferred term 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 severity, the event with the maximum severity will be used to summarize AEs by severity (likewise for relationship). Treatment-related TEAEs will be defined as those that the Investigator considers related to the IP.

The following summary tables will be produced:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- TEAEs related to study procedures
- TEAEs related to the underlying disease
- SAEs

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

The following listings will be produced:

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

13.8.2.2. Physical Examinations, Vital Signs, Height, and Weight

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

Data obtained from physical examinations will be presented in patient data listings. Any clinically significant findings will be recorded as AEs.

13.8.2.3. Clinical Safety Laboratory Tests

Clinical chemistry, hematology, renal function, coagulation, and urinalysis will be presented by visit for each age cohort and overall, summarizing the actual value 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 to abnormal of select laboratory parameter values will be generated.

13.8.2.4. Electrocardiograms

The actual value and change from baseline to each visit will be presented by visit for each age cohort and overall, summarizing the actual values and change from baseline to each visit for each parameter using descriptive statistics.

13.8.2.5. Echocardiograms

ECHO parameters, including the LVEF value and change from baseline in LVEF to each visit, will be summarized by visit for each age cohort and overall.

13.8.2.6. Prior and Concomitant Medications and Physiotherapeutic Interventions

All prior medications (including prior DMD medication) and concomitant medications, as well as physiotherapeutic interventions, will be presented in data listings.

13.9. [redacted]

[redacted]

13.10. Pharmacokinetic Analysis

Results of all PK analyses will be provided as a separate PK report which will be appended to the final CSR and summarized in the CSR.

Pharmacokinetic parameters of eteplirsen will be determined from plasma and urine concentration data. Individual plasma and urine levels of eteplirsen will be listed with the corresponding time relative to eteplirsen administration, and summary statistics will be generated by per-protocol time of collection. PK parameters for eteplirsen will be calculated using non-compartmental analysis and/or using population PK methodology, as appropriate. 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 and urine concentrations will be listed. PK parameters in plasma and urine will be summarized by dose level and age cohort. Plasma concentrations will be plotted versus elapsed time for dose level means and for individual patients. Dose proportionality will be evaluated across the range of doses studied.

13.11. Interim Analysis

An interim analysis of the PK and safety data following completion of dose escalation for one or both age cohorts may be done for administrative purposes. Detailed plans for data analysis will be documented in the study SAP or in a separate SAP for interim analysis only.

13.12. Other Statistical Issues

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

14. SPECIAL REQUIREMENTS AND PROCEDURES

14.1. Compliance with Ethical and Regulatory Guidelines

This study will comply with ICH-GCP, with the latest version of the Helsinki declaration and with applicable national regulations, as well as with the European Union Directive 2001/20/EC.

14.2. Institutional and Ethics Review

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 all substantial changes to the trial documentation will be subjected to the same IRB/IEC and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the IP during the study. IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB/IEC and the regulatory authority should be retained in the study regulatory files.

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

Written informed consent from each patient, patient's parent(s) or legal guardian(s), must be obtained prior to any study-specific screening evaluations being performed. A copy of the signed informed consent documents will be given to the patient, patient's parent(s) or legal guardian(s); 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 per regional requirements.

14.4. Compliance with the Protocol

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

14.5. Confidentiality

14.5.1. Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, with the exception of

information that is required by law or regulations to be disclosed to the IRB/IEC, the patient's parent(s) or legal guardian(s) or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act (HIPAA) standards and/or European standards.

14.5.2. Patient Confidentiality

The anonymity of participating patients will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. Patients may be referenced by their initials and an assigned patient identification number on the eCRFs 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.

15. STUDY DOCUMENTATION AND GENERAL INFORMATION

15.1. Essential Study Documents

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

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

15.2. General Information

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

15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics, Inc. However, at the conclusion of this clinical study, a CSR 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 the EudraCT database and on ClinicalTrials.gov. After completion of the study, results will be disseminated in accordance with regional requirements.

15.4. Product Handling and Complaints Reporting

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

16. LIST OF REFERENCES

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

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

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

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

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

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

Connolly AM, Florence JM, Cradock MM, Malkus EC, Schierbecker JR, Siener CA, et al. Motor and cognitive assessment of infants and young boys with Duchenne muscular dystrophy: results from the Muscular Dystrophy Association DMD Clinical Research Network. Neuromuscul Disord. 2013;23(7):529-39.

[redacted]

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

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

[redacted]

Howie, SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89:46-53.

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-67.

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

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

Mazzone E, Vasco G, Sormani MP, Torrente Y, Berardinelli A, Messina S, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology. 2011;77(3):250-6.

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

PTC Therapeutics International Limited. Summary of Product Characteristics for Translarna (ataluren) in the European Public Assessment Report (last updated 14 January 2016). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002720/human_med_001742.jsp&mid=WC0b01ac058001d124

17. APPENDICES

17.1. Estimated Blood Volumes to be Drawn

World Health Organization (WHO) recommended blood volume limits should be used as a guide for blood sampling in this study (Howie 2011). Per individual, the study-related blood loss should not exceed 3% of the total volume during a 4-week period or 1% of total blood volume within a 24-hour period. Table 6 summarizes the mean blood volume per body weight for children ≤10 kg and Table 7 summarizes the amount of blood required for individual sample collection.

Due to the limitations on the volume of blood collection that is considered to be acceptable in young children with very small total circulating blood volumes, adjustments to sample collection will be made for children weighing <10 kg. These adjustments include the use of 0.5 mL collection tubes for PK samples and utilization of local laboratories for the coagulation panel.

Table 6: Mean Blood Volume per Body Weight

Body Weight (kg)	Mean Total Body Blood Volume (mL)	Maximum Blood Collection Volume (mL)	
		24-Hour Period (1%)	30-Day Period (3%)
5.0	400	4.0	12.0
6.0	480	4.8	14.4
7.0	560	5.6	16.8
8.0	640	6.4	19.2
9.0	720	7.2	21.6
10.0	800	8.0	24.0

Table 7: Blood Volume Requirements per Test

Test	Volume (mL)
Chemistry panel	2.0
Hematology panel	1.0
Coagulation panel[a]	2.7
DMD sequencing	2.0
LTBP4 and SPP-1	2.0
PK (per sample)[b]	1.0

DMD = Duchenne muscular dystrophy; LTBP4 = latent transforming growth factor beta binding protein 4; PK = pharmacokinetic; SSP-1 = secreted phosphoprotein 1.

[a] Can be done at local laboratory in the event of blood volume limitations

[b] 0.5 mL for children weighing <10.0 kg

Source:

Howie, SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89:46-53. doi:10/2471/BLT.10.080010. Available from: http://www.who.int/bulletin/volumes/89/1/10-080010/en/