CLINICAL STUDY PROTOCOL

DRUG:	Eteplirsen (AVI-4658)
PROTOCOL NUMBER:	4658-301
PROTOCOL TITLE:	An Open-Label, Multicenter, Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy
IND NUMBER:	CCI [redacted]
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	02 June 2017, Version 5 (Amendment 4)

[redacted]

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	An Open-Label, Multicenter, Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy
Study No:	4658-301
Current Version Date:	02 June 2017 (Version 5, Amendment 4)

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

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

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

PPD

PPD

MD MS

PPD

PPD

PPD

Date

INVESTIGATOR'S AGREEMENT

I have read Protocol No. 4658-301 (Version 5, Amendment 4) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Responsible Physician	PPD MD, MS	PPD Telephone: PPD Mobile: PPD PPD

1. STUDY SYNOPSIS

NAME OF COMPANY Sarepta Therapeutics Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** Eteplirsen Injection **NAME OF ACTIVE INGREDIENT** Eteplirsen
TITLE: An Open-Label, Multicenter, Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy	
PROTOCOL NUMBER: 4658-301	
PHASE OF STUDY: Phase 3	
INVESTIGATOR STUDY SITES: This study will be conducted at approximately 35 study sites in North America.	

OBJECTIVES:

The primary objective of this study is to evaluate the effect of eteplirsen on ambulation, endurance, and muscle function as measured by change from Baseline to 96 weeks in the 6-minute walk test (6MWT) as compared to an untreated control arm of Duchenne muscular dystrophy (DMD) patients amenable to exon skipping.

The secondary objectives are to evaluate:

- the effect of eteplirsen on dystrophin expression as measured by the change from pretreatment in percentage of dystrophin-positive fibers (immunofluorescence histochemistry [IHC]) and dystrophin quantification by Western blot in biopsied muscle tissue
- the effect of eteplirsen on respiratory muscle strength as measured by the difference in change from Baseline in forced vital capacity % predicted and in maximal inspiratory and expiratory pressure % predicted between the eteplirsen treated and the untreated control arm of DMD patients amenable to exon skipping
- the safety and tolerability of eteplirsen

The additional objective is to evaluate the clinical and pharmacodynamic effects of eteplirsen treatment for up to 96 weeks.

METHODOLOGY:

This is an open-label, multicenter study to evaluate the efficacy and safety of eteplirsen in patients with genotypically confirmed DMD with exon deletions amenable to exon 51 skipping (treated group), with an untreated control arm of DMD patients amenable to exon skipping (untreated control group).

Patients will be evaluated for inclusion during a Screening/Baseline period of up to 10 weeks (not including time needed for genotyping if the patient has not been previously genotyped). Eligible patients for the treated group will receive once weekly intravenous (IV) infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into a separate eteplirsen study. Eligible patients for the untreated control group will not receive treatment with eteplirsen, but will complete study assessments through 96 weeks.

For all patients, efficacy, including the 6MWT, will be assessed at regularly scheduled study visits by a blinded rater. To minimize assessment bias, every effort will be made to keep the clinical evaluators unaware of the treatment arm of the patients, and all biological efficacy endpoint evaluations will be

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performed by blinded assessors. Upon qualification for the study during the Baseline visit, patients in the treated group will undergo a muscle biopsy, and will be randomized to a second muscle biopsy at Week 24, 48, 72, or 96 in a 1:2:1:1 ratio. Patients in the untreated control group will not undergo muscle biopsy at any time point.

Safety will be monitored for all patients throughout the study through the collection of adverse events (AEs), concomitant medications, physiotherapeutic interventions, laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations.

Blood samples for assessing plasma drug concentrations will be obtained at a subset of sites from at least 24 patients in the treated group. On Week 1, a single predose blood sample will be taken within 2 hours prior to the start of administration of the first dose. Both predose and postdose samples will be taken on Weeks 40, 48, 60, 84, and 96 as follows: within 2 hours prior to the start of the infusion, and approximately 5 to 10 minutes, 1 to 2 hours, and 2 to 4 hours after completion of the infusion; at Weeks 48 and 96, samples will also be taken at the end of the infusion prior to flushing the infusion line. Postdose samples alone will be taken on Weeks 8, 16, 24, 32, and 72, approximately 5 to 10 minutes after the completion of the infusion (the approximate time of post-dosing maximum plasma concentration for eteplirsen). Additional post dose samples will be taken on Weeks 8 and 24, approximately 1 to 2 hours after the completion of the infusion and on Week 72 at 2 to 4 hours after the completion of the infusion.

DURATION OF STUDY:

Screening/Baseline Period: up to 10 weeks (not including time needed for genotyping if the patient has not previously been genotyped)

Treatment Period: at least 96 weeks

Safety Extension: not to exceed 48 weeks

Safety Follow-up Period: 4 weeks following the last infusion

Total patient participation: approximately 158 weeks

NUMBER OF PATIENTS: Approximately 110 patients will be included in this study, including approximately 90 patients with a Baseline 6MWT distance between 300 and 450 meters (~70 patients in the treated group and ~20 patients in the untreated control group) and approximately 20 patients with a Baseline 6MWT distance >450 meters (~10 patients in the treated group and ~10 patients in the untreated control group).

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

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

1. Be a male with DMD and meet one of the following criteria:
   - Have an out-of-frame deletion that may be treated by exon 51 skipping (e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63). These patients will be enrolled into the treated group.
   - Have an out-of-frame deletion that is <u>not</u> amenable to treatment by exon 51 skipping but is amenable to treatment by skipping other exons (i.e., whole exon deletions in which the

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reading frame may be restored by skipping 1 or 2 exons). These patients will be enrolled into the untreated control group.

2. Be 7 to 16 years of age, inclusive.
3. Have stable pulmonary function (forced vital capacity [FVC] % of predicted ≥50% and not require nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Have intact right and left bicep muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Have been on a stable dose of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: patients may be allowed to take other (non-ribonucleic acid [RNA] antisense or non-gene therapy) medication including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β blockers, potassium, and coenzyme Q, provided they have been on a stable dose for 24 weeks prior to Week 1 and the dose is expected to remain constant throughout the study.
6. Achieve a mean distance of 2 separate assessments on 2 consecutive days at the Screening and Baseline visits (prior to Week 1) ≥300 meters on the 6MWT with the 2 consecutive means being within 15% of each other, and with the Screening and Baseline 6MWT conducted 3 to 5 weeks apart. Personal assistance or use of any assistive devices for ambulation is not permitted during the 6MWT.
7. Male patients who are in the treated group and are post-pubertal and sexually active must agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g., oral contraceptives).
8. Have a parent(s) or legal guardian(s) who is able to understand and comply with all the study requirements.
9. Be willing to provide informed assent (if applicable) and have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

Exclusion Criteria

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

1. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks of Week 1 that may have an effect on muscle strength or function (e.g., growth hormone, anabolic steroids).
2. Previous treatment with ezutromid (BMN 195/SMT C1100) at any time.
3. Previous treatment with drisapersen (PRO051) therapy within the last 3 months. To be eligible for the study, patients who were previously treated with drisapersen must be free of any of the following prior to Week 1: a) any active skin lesions related to drisapersen injection; b) renal signs/symptoms (including proteinuria or elevated creatinine/cystatin C); c) the presence of anti-platelet antibodies (to be tested at screening for patients who were previously treated with drisapersen); and d) abnormal platelet count.

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4. Previous treatment with any other RNA antisense agent or any gene therapy within the last 6 months, or participation in any other DMD interventional clinical study within 12 weeks of Week 1, or use of the shock training system or "STS," or planned use during this study. Concurrent enrollment in any natural history, observational, or biomarker clinical trial is permitted, provided the patient's participation in the other trial does not affect any of the assessments performed in the 4658-301 clinical study. For patients in the untreated control group only, continuation in an interventional trial with standard-of-care medication may also be permitted if the patient's participation in the standard-of-care interventional trial does not affect any of the assessments performed in Study 4658-301, and the patient meets all the protocol-required entry criteria.
5. Major surgery within 3 months of Week 1, or planned surgery for any time during this study, except for protocol-specified surgeries, as applicable.
6. Presence of other clinically significant (CS) illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease, or malignancy.
7. Use of any aminoglycoside antibiotic within 12 weeks of Week 1 or need for use of an aminoglycoside antibiotic or statin during the study.
8. Have a left ventricular ejection fraction (LVEF) of <50% based on the screening ECHO or QTcF ≥450 msec based on the screening ECG.
9. Loss of ≥30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (i.e., fixed plantar flexion of 10 degrees or more).
10. Change in contracture treatment such as serial casting, contracture control devices, night splints, stretching exercises (passive, active, self) within 3 months prior to enrollment, or expected need for such intervention during the study.
11. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, patients who seem unwilling to comply with the study procedures, in the Investigator's opinion, are to be excluded.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Eteplirsen 30 mg/kg will be administered as an IV infusion once a week for at least 96 weeks in the treatment period, and for up to 48 weeks in the safety extension.

REFERENCE TREATMENT:

The control group will be untreated.

CRITERIA FOR EVALUATION:

Efficacy:

The primary efficacy endpoint is the change from Baseline to Week 96 in 6MWT.

The secondary efficacy endpoints are the:

- Change from Baseline in dystrophin protein levels quantified by Western blot (treated patients only)

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- Change from Baseline in dystrophin intensity levels determined by immunofluorescence (treated patients only)
- Ability to rise independently from the floor (without external support) as indicated by a North Star Ambulatory Assessment (NSAA) subscore of "2" (without modification) or "1" (Gower's maneuver)
- Loss of ambulation
- Change from Baseline in FVC % predicted
- Change from Baseline in NSAA total score

CCI [redacted]

SAFETY:

The safety and tolerability of eteplirsen will be assessed through evaluation of: the type, frequency, severity, timing, and relationship to investigational product of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation; concomitant medications and physiotherapeutic interventions; clinical laboratory testing including chemistry, hematology, coagulation, and urinalysis; vital signs; physical examinations; ECG; and ECHO (ejection fraction and fractional shortening).

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Pharmacokinetics:

Standard pharmacokinetic (PK) parameters will be estimated based on sparse sampling. The effects of demographic characteristics, concomitant medications, laboratory values, and other covariates on eteplirsen PK will be evaluated.

SAMPLE SIZE:

This study will enroll approximately 90 patients with Baseline 6MWT distance of 300 to 450 meters, including approximately 70 patients in the eteplirsen-treated group and approximately 20 patients in the untreated control group. CCI [redacted]

Additionally, approximately 20 patients (10 treated vs 10 untreated control) with Baseline 6MWT distance of >450 meters will be enrolled.

STATISTICAL METHODS:

Analysis of Efficacy Endpoints

The efficacy set for primary efficacy analyses will be patients with a baseline 6MWT distance of 300 to 450 meters, inclusive.

The analysis of change from Baseline to Week 96 (the primary time point of interest) in the 6MWT will be based on a mixed model repeated measures (MMRM) analysis, with treatment group, time, time by treatment group interaction, baseline 6MWT distance, and baseline 6MWT distance by time interaction as fixed effects; and patient as a random effect. Additional baseline variables may be added as covariates in the Statistical Analysis Plan (SAP). A heterogeneous autoregressive (1) variance-covariance matrix will be used. Estimates for changes from Baseline at each time point in each treatment group and for treatment differences will be provided with 95% confidence intervals and descriptive p-values using appropriate contrasts from the model. Due to the potential difference in progression based on DMD genotype in the control group, notably those with deletions amenable to skipping exon 44, additional sensitivity analyses may be performed.

As muscle biopsies will be confined to the treated group, the analysis of the secondary endpoints of change from Baseline in dystrophin protein levels by Western blot and dystrophin intensity levels determined by immunofluorescence will be based on a 1-sample permutation t-test. The analysis of the secondary endpoints of time from Baseline to loss of the ability to rise independently (from supine to standing) and time to loss of ambulation will be analyzed using the Kaplan-Meier method. The analyses of the secondary efficacy endpoints of change from Baseline in FVC % predicted and change from Baseline in NSAA total score will be similar to the primary endpoint.

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All efficacy data will be summarized descriptively by visit and treatment group.

Safety Analyses

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

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

Pharmacokinetic Analyses

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

PK analysis of plasma concentration-time data of eteplirsen will be performed using nonlinear mixed-effects modeling. For population PK analyses, PK data from this study may be combined with those of other studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, concomitant medications, etc.) will be tested as potential covariates affecting PK parameters.

Interim Analysis

An interim analysis will be performed after approximately 35 patients with Baseline 6MWT between 300 and 450 meters, inclusive, have completed their Week 96 assessments. Given the small size of the untreated control group, external control patients, including those amenable to exon 51 skipping, may be identified and compared to the eteplirsen-treated group. The details of the interim analysis will be specified in a Statistical Analysis Plan before the database lock for the interim analysis.

2. SCHEDULE OF EVENTS

Table 2: Schedule of Events for Patients in the Treated Group - Screening Through Week 48

Assessments	**Up to 10 weeks prior to Week 1[a]**			**Treatment Period[b] (2-day HS visits occur at Weeks 12, 24, 36, and 48)**												
Study Period	**Screening -10w up to -3w**		**Baseline -4w to Day -1&-2**													
Week	**1-day visit**	**2-day visit**	**2-day visit (3-5w after Screening at HS)**	**W1[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**
Informed consent for screening at local site	X															
Informed consent for screening at HS (if different from local site)		HS														
Informed consent for biopsies			SU													
Informed consent to participate as a treated patient (no consent form needed at W12 if local is same as HS)[d]				X			HS									
Assess inclusion/exclusion criteria	X	HS	HS													
Confirm eligibility and Randomization[d]			X	X												
Medical history	X															

Table 2: Schedule of Events for Patients in the Treated Group - Screening Through Week 48, continued

Assessments	Up to 10 weeks prior to Week 1[a]			Treatment Period (2-day HS visits occur at Weeks 12, 24, 36, and 48)												
Study Period	Screening -10w up to -3w		Baseline -4w to Day -1&-2													
Week	1-day visit	2-day visit	2-day visit (3-5w after Screening at HS)	W1[c]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48[c]
Full physical examination[e]	X			X	X		X			X			X			X
Brief physical examination[e]						X		X	X		X	X		X	X	
Vital signs[f]	X		HS	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory assessments[g]	X[h]		SU	X[h]	X	X	X			X			X			X
Immunogenicity			SU	X	X	X	X			X			X			X
CCI																
PK sampling predose[i]				X										X		X
PK sampling postdose[i]						X		X		X		X		X		X
Whole blood for DMD genotyping	X															
CCI																
Height (and ulnar length at HS visits)	X		HS				HS			HS			HS			HS
6MWT[j]		HS	HS				HS			HS			HS			HS
NSAA[j]			HS				HS			HS			HS			HS
CCI																

Table 2: Schedule of Events for Patients in the Treated Group - Screening Through Week 48, continued

Assessments	Up to 10 weeks prior to Week 1[a]			Treatment Period (2-day HS visits occur at Weeks 12, 24, 36, and 48)												
Study Period	Screening -10w up to -3w		Baseline -4w to Day -1&-2													
Week	1-day visit	2-day visit	2-day visit (3-5w after Screening at HS)	W1[c]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48[c]
CCI																
ECG[l]		HS	HS				HS			HS			HS			HS
ECHO[l]		HS								HS						HS
Muscle biopsy[m]			SU							SU						SU
Eteplirsen infusion[n]				Once Weekly ± 3 days (to be scheduled based on Week 1 infusion date) at Local Site												
Conmed/therapy	Continuous															
AE assessment	Continuous															

X = Local Site, HS = Hub Site, SU = Surgical Unit
Assessments at Hub Sites and Surgical Units have a ±2 week window and will occur at least 48 hours following an infusion.

a. Not including the time needed for genotyping if the patient has not previously been genotyped. If the patient has not been previously genotyped, then no other screening procedures other than informed consent and genotyping may be done until results of genotyping are known, at which time the 10-week Screening period will begin.
b. An Early Termination visit is required (see W96 procedures) if the patient discontinues more than 4 weeks after a Functional Assessment visit (Week 12, 24, 36, 48, or 72).
c. Week1 should occur within 4 weeks of the Baseline Functional Assessment visit (performed at the Hub Site). If the Week 1 visit is more than 4 weeks after Baseline, the patient is required to repeat the Baseline functional assessments. The repeated 6MWT assessment must be within 15% of the previous Baseline assessment in order to meet eligibility.
d Eligibility will be assessed during Screening and confirmed by the Local Site after completion of the 6MWT at the Baseline visit. Upon qualification for the study during the Baseline visit, patients in the treated group will be randomized to a muscle biopsy schedule. Eligibility will be reconfirmed at Week 1 based on all available data including safety laboratory assessments.
e Full physical examination: general appearance, head, eyes, ears, nose, and throat (HEENT), heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems. Brief physical examination: general appearance, HEENT, heart, chest, abdomen, and skin.

Table 2: Schedule of Events for Patients in the Treated Group - Screening Through Week 48, continued

Assessments	Up to 10 weeks prior to Week 1[a]			Treatment Period (2-day HS visits occur at Weeks 12, 24, 36, and 48)												
Study Period	Screening -10w up to -3w		Baseline -4w to Day -1&-2													
Week	1-day visit	2-day visit	2-day visit (3-5w after Screening at HS)	W1[c]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48[c]

f Vital signs include blood pressure, heart rate, respiration, and oral temperature. On infusion days, vital signs will be measured 30 minutes prior to infusion and 5, 30, and 60 minutes after the end of the infusion. Vital signs should be collected as close to or at the exact indicated times as possible.

g Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

h Patients who were previously treated with drisapersen will be tested for anti-platelet antibodies at Screening, and must have a normal platelet count prior to Week 1.

i PK sampling is only applicable at a subset of sites for patients in the treated group.

Predose sample only: On Week 1, a single blood sample will be taken within 2 hours prior to the start of the administration of the first dose.

Both predose and postdose samples: Both predose and postdose samples will be taken on Weeks 40 and 48 as follows: within 2 hours prior to the start of the infusion and approximately 5 to 10 minutes, 1 to 2 hours, and 2 to 4 hours after the completion of the infusion. An additional sample will be taken at Week 48 at the end of the infusion prior to flushing the infusion line.

Postdose samples only: On Weeks 8, 16, 24, and 32, a postdose sample will be taken approximately 5 to 10 minutes after the completion of the infusion (the approximate time of post-dosing maximum plasma concentration for eteplirsen). Additional postdose samples will be taken at Weeks 8 and 24 at approximately 1 to 2 hours after the completion of the infusion.

j The 6MWT and NSAA will be performed on 2 consecutive days and may require 2-night overnight stays. Pulse will be obtained prior to and immediately after the 6MWT.

CCI [redacted]

l ECG and ECHO may be performed on either day of the specified 2-day visits during the treatment period.

mProcedure is only applicable for patients who qualify for the treated group and will occur at the surgical unit (SU). Upon qualification for the study during the Baseline visit, patients in the treated group will be randomized to 1 of 4 biopsy groups according to this muscle biopsy schedule: 1) biopsy at Baseline and Week 24, 2) biopsy at Baseline and Week 48, 3) biopsy at Baseline and Week 72, or 4) biopsy at Baseline and Week 96. The biopsies at Weeks 24, 48, 72, and 96 must occur within 2 weeks after the specified visit, after the clinical evaluation, and at least 48 hours after the most recent infusion.

n Eteplirsen will be administered by IV infusion. Patients should be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5% or LMX4 cream) be applied prior to infusions. Patients who discontinue treatment with eteplirsen will have an End of Study visit (see W148 procedures) 4 weeks after their last infusion.

Table 3: Schedule of Events for Patients in the Treated Group - Week 49 Through Week 96

Assessments / Study Period	Treatment Period[a] (2-day HS visits occur at Weeks 72 and 96)												
Week	**W49**	**W52**	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96/ ET[a]**
Full physical examination[b]							X						X
Brief physical examination[b]		X	X	X	X	X		X	X	X	X	X	
Vital signs[c]	Weekly												
Weight		X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory assessments[d]							X						X
Immunogenicity				X			X			X			X
CCI													
PK sampling predose[e]				X						X			X
PK sampling postdose[e]				X			X			X			X
Height and ulnar length							HS						HS
6MWT[f]							HS						HS
NSAA[f]							HS						HS
CCI													

Table 3: Schedule of Events for Patients in the Treated Group - Week 49 Through 96, continued

Assessments / Study Period	Treatment Period[a] (2-day HS visits occur at Weeks 72 and 96)												
Week	W49	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96/ ET[a]
ECG[h]							HS						HS
ECHO[h]							HS						HS
Muscle biopsy[i]							SU						SU
Eteplirsen infusion[j]	Once Weekly ± 3 days (to be scheduled based on Week 1 infusion date) at Local Site												
Conmed/therapy	Continuous												
AE assessment	Continuous												

X = Local Site, HS = Hub Site, SU = Surgical Unit

Assessments at Hub Sites and Surgical Units have a ±2 week window and will occur at least 48 hours following an infusion.

a Early termination assessments are the same as Week 96 assessments. An Early Termination visit is required if the patient discontinues more than 4 weeks after a Functional Assessment visit (Week 12, 24, 36, 48, or 72).

b Full physical examination: general appearance, head, eyes, ears, nose, and throat (HEENT), heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems. Brief physical examination: general appearance, HEENT, heart, chest, abdomen, and skin.

c Vital signs include blood pressure, heart rate, respiration, and oral temperature. On infusion days, vital signs will be measured 30 minutes prior to infusion and 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be reduced to pre-infusion and 30 minutes after the end of the infusion. Vital signs should be collected as close to or at the exact indicated times as possible.

d Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

e PK sampling is only applicable at a subset of sites for patients in the treated group.
Both predose and postdose samples: Both predose and postdose samples will be taken on Weeks 60, 84, and 96 as follows: within 2 hours prior to the start of the infusion, and approximately 5 to 10 minutes, 1 to 2 hours, and 2 to 4 hours after completion of the infusion. An additional sample will be taken at Week 96 at the end of the infusion prior to flushing the infusion line.
Postdose samples only: On Week 72, a postdose sample will be taken approximately 5 to 10 minutes after the completion of the infusion (the approximate time of post-dosing maximum plasma concentration for eteplirsen) and again within 2 to 4 hours after the completion of the infusion.

f The 6MWT and NSAA will be performed on 2 consecutive days and may require 2-night overnight stays. Pulse will be obtained prior to and immediately after the 6MWT.

CCI [redacted]

h ECG and ECHO may be performed on either day of the specified 2-day visits during the treatment period.

Table 3: Schedule of Events for Patients in the Treated Group - Week 49 Through 96, continued

Assessments / Study Period	Treatment Period (2-day HS visits occur at Weeks 72 and 96)												
Week	W49	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96/ ET[a]

i Procedure is only applicable for patients who qualify for the treated group and will occur at the surgical unit (SU). Upon qualification for the study during the Baseline visit, patients in the treated group will be randomized to 1 of 4 biopsy groups according to this muscle biopsy schedule: 1) biopsy at Baseline and Week 24, 2) biopsy at Baseline and Week 48, 3) biopsy at Baseline and Week 72, or 4) biopsy at Baseline and Week 96. The biopsies at Weeks 24, 48, 72, and 96 must occur within 2 weeks after the specified visit, after the clinical evaluation, and at least 48 hours after the most recent infusion.

j Eteplirsen will be administered by IV infusion. Patients should be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5% or LMX4 cream) be applied prior to infusions. Optional in-home administration of eteplirsen by a visiting nurse may be available after Week 25 for visits where safety assessments are not being collected.

Table 4: Schedule of Events for Patients in the Treated Group – Safety Extension (Week 97 through End of Study)

Assessments / **Study Period**	**Safety Extension[a]**					**End of Study**
Week	**Week 97**	**W108**	**W120**	**W132**	**W144**	**W148/ET[b]**
Full physical examination[c]			X		X	X
Vital signs[d]	Weekly					X
Weight	Every 4 weeks					X
Safety laboratory assessments[e]			X		X	X
Eteplirsen infusion[f]	Once Weekly ± 3 days (to be scheduled based on Week 1 infusion date) at Local Site					
Conmed/therapy	Continuous					
AE assessment	Continuous					

X = Local Site

a Patients may continue in the safety extension for up to 48 weeks, until the product is commercially available or until they can transition into a separate eteplirsen study.

b Early termination assessments are the same as Week 144 assessments.

c Full physical examination: general appearance, head, eyes, ears, nose, and throat (HEENT), heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems.

d Vital signs include blood pressure, heart rate, respiration, and oral temperature. On infusion days, vital signs will be measured prior to infusion and approximately 5 and 30 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be reduced to pre-infusion and 30 minutes after the end of the infusion.

e Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

f Eteplirsen will be administered by IV infusion. Patients should be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5% or LMX4 cream) be applied prior to infusions. Patients who discontinue treatment with eteplirsen will have an End of Study visit (see W148 procedures) 4 weeks after their last infusion. Optional in-home administration of eteplirsen by a visiting nurse may be available for visits where safety assessments are not being collected.

Table 5: Schedule of Events for Untreated Control Patients - Screening Through End of Study

Assessments	Up to 10 weeks prior to Week 1[a]			Observation Period[b] (2-day HS visits occur at Weeks 12, 24, 36, 48, 72, and 96)								
Study Period	Screening -10w up to -3w		Baseline -4w to Day -1&-2									
Week	1-day visit	2-day visit	2-day visit (3-5w after Screening at HS)	W1[c]	W4	W8	W12	W24	W36	W48	W72	W96/ ET[b]
Informed consent for screening at local site	X											
Informed consent for screening at HS (if different from local site)		HS										
Informed consent to participate as a control patient (no consent form needed at W12 if local is same as HS)				X			HS					
Assess inclusion/exclusion criteria	X	HS	HS									
Confirm eligibility[d]			X	X								
Medical history	X											
Full physical examination[e]	X			X	X		X	X	X	X	X	X
Brief physical examination[e]						X						
Vital signs[f]	X		HS	X	X	X	X	X	X	X	X	X
Weight	X			X	X	X	X	X	X	X	X	X
Safety laboratory assessments[g]	X[h]			X[h,i]	X	X	X	X	X	X	X	X

Table 5: Schedule of Events for Untreated Control Patients - Screening Through End of Study, continued

Assessments	Up to 10 weeks prior to Week 1[a]			Observation Period[b] (2-day HS visits occur at Weeks 12, 24, 36, 48, 72, and 96)								
Study Period	Screening -10w up to -3w		Baseline -4w to Day -1&-2									
Week	1-day visit	2-day visit	2-day visit (3-5w after Screening at HS)	W1[c]	W4	W8	W12	W24	W36	W48	W72	W96/ ET[b]
Immunogenicity				X[i]	X	X	X	X	X	X	X	X
CCI												
Whole blood for DMD genotyping	X											
CCI												
Height (and ulnar length at HS visits)	X		HS				HS	HS	HS	HS	HS	HS
6MWT[j]		HS	HS				HS	HS	HS	HS	HS	HS
NSAA[j]			HS				HS	HS	HS	HS	HS	HS
CCI												
ECG[l]		HS	HS				HS	HS	HS	HS	HS	HS
ECHO[l]		HS						HS		HS	HS	HS
Conmed/therapy	Continuous											
AE assessment	Continuous											

Table 5: Schedule of Events for Untreated Control Patients - Screening Through End of Study, continued

Assessments	Up to 10 weeks prior to Week 1[a]			Observation Period[b] (2-day HS visits occur at Weeks 12, 24, 36, 48, 72, and 96)								
Study Period	Screening -10w up to -3w		Baseline -4w to Day -1&-2									
Week	1-day visit	2-day visit	2-day visit (3-5w after Screening at HS)	W1[c]	W4	W8	W12	W24	W36	W48	W72	W96/ ET[b]

X = Local Site, HS = Hub Site

Functional assessments at Hub Sites beyond Week 1 have a ±2 week window.

Note: To reduce the burden on the untreated control patients, all protocol-specified assessments after Week 12 may be performed at the Hub Site. If a patient transfers to their assigned Hub Site for collection of safety assessments (e.g., laboratory assessments, vital signs, and physical examinations), the functional assessments must be done first, and the safety assessments should be done after completion of the functional assessments.

a Not including the time needed for genotyping if the patient has not previously been genotyped. If the patient has not been previously genotyped, then no other screening procedures other than informed consent and genotyping may be done until results of genotyping are known, at which time the 10-week Screening period will begin.

b Early termination assessments are the same as Week 96 assessments. An Early Termination visit is required if the patient discontinues more than 4 weeks after a Functional Assessment visit (Week 12, 24, 36, 48, or 72).

c Week 1 should occur within 4 weeks of the Baseline Functional Assessment visit (performed at the Hub Site). If the Week 1 visit is more than 4 weeks after Baseline, the patient is required to repeat the Baseline functional assessments. The repeated 6MWT assessment must be within 15% of the previous Baseline assessment in order to meet eligibility.

d Eligibility will be assessed during Screening and confirmed by the local site after completion of the 6MWT at the Baseline visit. Eligibility will be reconfirmed at Week 1 based on all available data including safety laboratory assessments.

e Full physical examination: general appearance, head, eyes, ears, nose, and throat (HEENT), heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems. Brief physical examination: general appearance, HEENT, heart, chest, abdomen, and skin.

f Vital signs include blood pressure, heart rate, respiration, and oral temperature.

g Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

h Patients who were previously treated with drisapersen will be tested for anti-platelet antibodies at Screening, and must have a normal platelet count prior to Week 1.

i Samples obtained at Week 1 are considered Baseline for the untreated control group.

j The 6MWT and NSAA will be performed on 2 consecutive days and may require 2-night overnight stays. Pulse will be obtained prior to and immediately after the 6MWT.

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l ECG and ECHO may be performed on either day of the specified 2-day visits during the treatment period.

3. TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2D	2 dimensional
6MWT	6-Minute Walk Test
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocking agent
AST	aspartate aminotransferase
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CD	compact disc
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CK	creatine kinase
CLIA	Clinical Laboratory Improvement Act
CRF	case report form
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
EDC	electronic data capture
EF	ejection fraction
FDA	US Food and Drug Administration
FS	fractional shortening
FVC	forced vital capacity
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
HEENT	head, ears, eyes, nose, throat

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IHC	immunofluorescence histochemistry
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous, intravenously
KIM-1	kidney injury molecule-1
LDH	lactate dehydrogenase
[redacted]	CCI [redacted]
LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities®
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
mITT	modified Intent-to-Treat
CCI	[redacted]
MMRM	mixed model repeated measures
mRNA	messenger ribonucleic acid
CCI	[redacted]
NCS	non-clinically significant
NSAA	North Star Ambulatory Assessment
CCI	[redacted]
PK	pharmacokinetic
PMO	phosphorodiamidate morpholino oligomer
CCI	[redacted]
PT	Preferred Term
CCI	[redacted]
QTcF	QT interval corrected by Fridericia's correction
RBC	red blood cells
RNA	ribonucleic acid

Abbreviation	Definition
CCI [redacted]	[redacted]
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
[redacted]	CCI [redacted]
STS	shock training system
SUSARS	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cell

5. INTRODUCTION AND RATIONALE

5.1. Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare (estimated incidence of 1 in 3,500-5000 live births; CDC 2009; Emery 1991), degenerative, X-linked recessive genetic disorder caused by mutations in the dystrophin gene. In DMD, mutations in the dystrophin gene disrupt the open-reading frame, resulting in an absence of functional dystrophin, a critically important part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contraction causes cellular degeneration, regeneration, and inflammation, and, over time, myonecrosis.

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

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

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

Phosphorodiamidate morpholino oligomers (PMOs) are a class of synthetic molecules based on a redesign of the natural nucleic acid structure. PMOs are distinguished from other antisense oligonucleotide platforms due to the use of a 6-member, synthetic morpholine ring (opposed to the 5-member ribose rings in ribonucleic acid [RNA] and deoxyribonucleic acid [DNA]) to bind the nucleobases, and the morpholine rings are linked through CCI [redacted] phosphorodiamidate moieties CCI [redacted]. These differences impart the stability and safety observed with these compounds in nonclinical and clinical studies.

PMOs are capable of in vivo binding to pre-messenger RNA (pre-mRNA) in a sequence-specific fashion with sufficient avidity to alter the splicing of a pre-mRNA transcript, such as dystrophin. Seventy-five percent (75%) of boys with DMD have out-of-frame deletions that could be amenable to exon skipping therapies (Aartsma-Rus 2009), and modulation of pre-mRNA splicing by exon skipping is currently the most promising molecular intervention in DMD.

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

5.3. Clinical Experience with Eteplirsen

Two Phase 1 clinical studies of eteplirsen have provided initial support and proof-of-concept for the safety and potential efficacy of eteplirsen in the treatment of DMD. In light of the positive findings from these early clinical studies, a double-blind, placebo-controlled Phase 2 study (Study 4658-us-201) was initiated. This study randomized 12 patients aged 7 to 13 years to receive once weekly infusions of eteplirsen or placebo as follows: Group 1 received 50 mg/kg eteplirsen for 28 weeks (n = 4); Group 2 received 30 mg/kg eteplirsen for 28 weeks (n = 4); Group 3a received placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks (n = 2); and Group 3b received placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks (n = 2).

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

Study 4658-us-202 met its primary biological efficacy endpoint of increased novel dystrophin as assessed by immunofluorescence histochemistry (IHC) in muscle (biopsies at Week 48). Results through more than 2 years in Study 4658-us-202 have shown a continued stabilization of walking ability in continuously eteplirsen-treated patients evaluable on the 6-Minute Walk Test (6MWT). At 120 weeks, patients in the 30 mg/kg and 50 mg/kg continuous-eteplirsen cohorts who were able to perform the 6MWT (n = 6, modified Intent-to-Treat [mITT]) experienced a decline of 13.9 meters (<5%) from Baseline in walking ability. (Note that 2 DMD boys lost their ambulation within the first months in Study 4658-us-201 due to disease progression. These boys were identical twins close to 10 years old who were excluded from the mITT population.) A statistically significant treatment benefit of 64.9 meters ($p \leq 0.006$) was observed for this group as compared to the placebo/delayed-treatment cohort (n = 4), which initiated treatment at Week 25 following 24 weeks of placebo. After experiencing a substantial decline earlier in the study, this placebo/delayed-treatment cohort also demonstrated stabilization in walking ability for more than 1.5 years (from Week 36 through Week 120), the period from which meaningful levels of

dystrophin were likely produced, with a decline of 9.5 meters over this timeframe. These analyses were based on the maximum 6MWT score when the test was performed on 2 consecutive days.

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

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

5.4. Rationale for the Current Study

The purpose of this study is to evaluate the efficacy and safety of eteplirsen in patients with genotypically confirmed DMD with exon deletions amenable to exon 51 skipping.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to evaluate the effect of eteplirsen on ambulation, endurance, and muscle function as measured by change from Baseline to 96 weeks in the 6MWT as compared to an untreated control arm of DMD patients amenable to exon skipping.

6.2. Secondary Objectives

The secondary objectives are to evaluate:

- The effect of eteplirsen on dystrophin expression as measured by the change from pretreatment in dystrophin quantification by Western blot and dystrophin intensity levels determined by immunofluorescence in biopsied muscle tissue
- The effect of eteplirsen on respiratory muscle strength as measured the difference in change from Baseline in forced vital capacity (FVC) % predicted and in maximal inspiratory and expiratory pressure % predicted between the eteplirsen treated and the untreated control arm of DMD patients amenable to exon skipping

The safety and tolerability of eteplirsen

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6.4. Pharmacokinetic Objective

The pharmacokinetic (PK) objective is to evaluate the PK properties of eteplirsen via a population PK model.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, multicenter, study to evaluate the efficacy and safety of eteplirsen in patients with genotypically confirmed DMD with exon deletions amenable to exon 51 skipping (treated group), as compared with an untreated control arm of DMD patients amenable to exon skipping (untreated control group).

Patients will be evaluated for inclusion during a Screening/Baseline period of up to 10 weeks (not including time needed for genotyping if the patient has not been previously genotyped). Eligible patients for the treated group will receive once weekly IV infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into a separate eteplirsen study. Eligible patients in the untreated control group will not receive treatment with eteplirsen, but will complete selected study assessments through 96 weeks.

For the treated group, eteplirsen will be administered once weekly via an IV infusion. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5% or LMX4 cream) be applied to the infusion site prior to each administration of eteplirsen. An implanted venous access port may be inserted for eteplirsen administration at the discretion of the parent/legal guardian and the Investigator. Patients should be observed for possible reactions to the infusion for at least 1 hour after each infusion is completed. For visits where safety assessments are not being collected, optional in-home administration of eteplirsen by a visiting nurse may be available after Week 25.

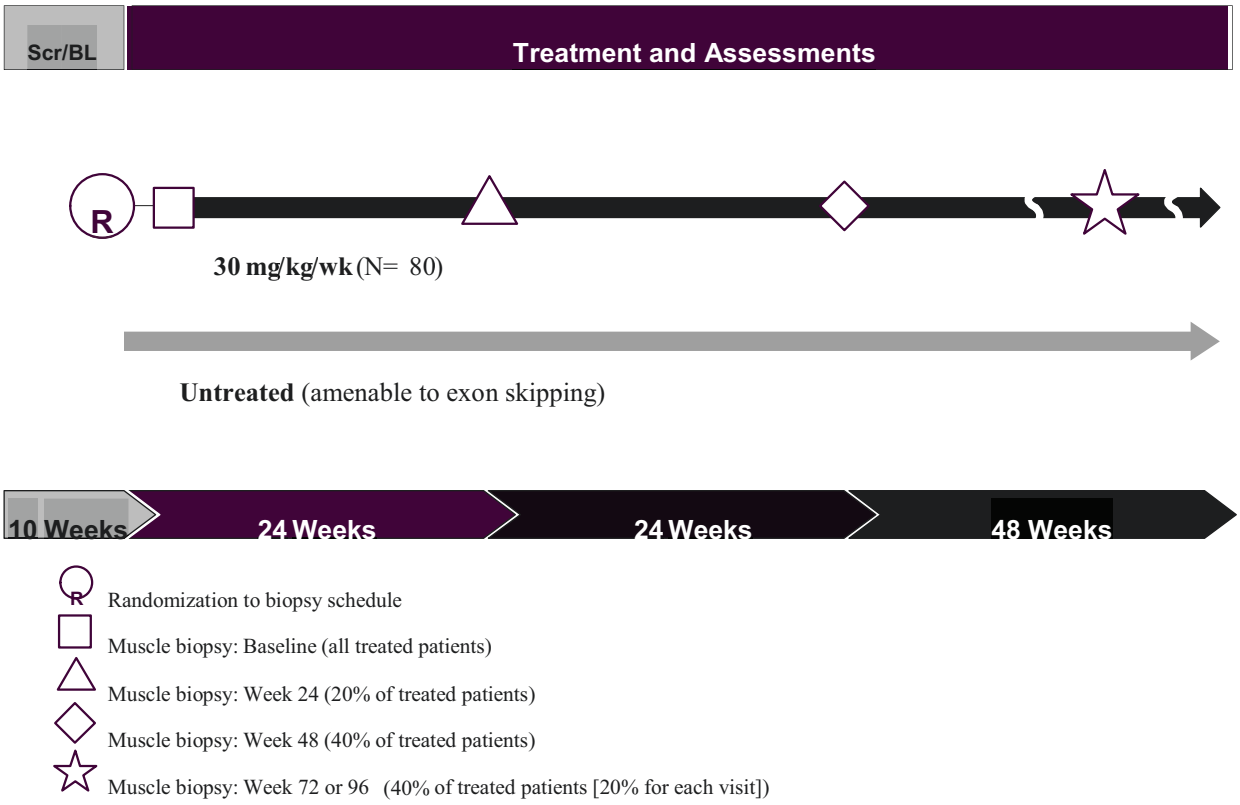
For all patients, efficacy, including the 6MWT, will be assessed at regularly scheduled study visits by a blinded rater. To minimize assessment bias, every effort will be made to keep the clinical evaluators unaware of the treatment arm of the patients, and all biological efficacy endpoint evaluations will be performed by blinded assessors. Upon qualification for the study during the Baseline visit, patients in the treated group will undergo a muscle biopsy and will be randomized to a second muscle biopsy at Week 24, 48, 72, or 96 in a 1:2:1:1 ratio. Patients in the untreated control group will not undergo muscle biopsy at any time point.

Safety will be monitored for all patients throughout the study through the collection of AEs, concomitant medications, physiotherapeutic interventions, laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations.

Blood samples for assessing plasma drug concentrations will be obtained at a subset of sites from at least 24 patients in the treated group according to the tables in Section 2.

An overview of the study design through Week 96 (i.e., excluding the safety extension) is presented in Figure 1.

Figure 1: Overview of Study Design through Week 96



7.2. Dose Selection Rationale

The dose of eteplirsen selected for this study, 30 mg/kg, was chosen based on results from the Phase 2, double-blind, placebo-controlled, multiple-dose study, Study 4658-us-201, and its open-label extension, Study 4658-us-202. As described in Section 5.3, these studies assessed the efficacy, safety, tolerability, and PK of 2 eteplirsen doses (50 mg/kg and 30 mg/kg) administered as IV infusions in 12 patients diagnosed with DMD with out-of-frame deletions amenable to treatment by skipping exon 51.

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

At Week 48, increases in the percent of dystrophin-positive fibers were similar for patients who had received weekly 30 and 50 mg/kg eteplirsen without interruption from Week 1 (52% and 42% of normal, respectively or 47% for the combined groups). These data suggest that the effect of eteplirsen on the production of novel dystrophin is not significantly different between the 2 doses tested in this study. Therefore, the lower dose was selected as the more conservative choice, because patients would receive this drug as a life-long treatment.

7.3. Study Endpoints

Unless otherwise, specified, the study endpoints apply to both the treated and control groups.

7.3.1. Efficacy Endpoints

7.3.1.1. Primary Efficacy Endpoint

- Change from Baseline to Week 96 in the 6MWT

7.3.1.2. Secondary Efficacy Endpoints

- Change from Baseline in dystrophin protein levels quantified by Western blot (treated patients only)
- Change from Baseline in dystrophin intensity levels determined by immunofluorescence (treated patients only)
- Ability to rise independently from the floor (without external support), as indicated by a North Star Ambulatory Assessment (NSAA) subscore of "2" (without modification) or "1" (Gower's maneuver)
- Loss of ambulation
- Change from Baseline in FVC% predicted
- Change from Baseline in NSAA total score

7.3.2. Safety Endpoints

The safety and tolerability of eteplirsen will be assessed through evaluation of:

- The type, frequency, severity, timing, and relationship to IP of treatment-emergent adverse events (TEAE), SAEs, and AEs leading to discontinuation.
- Concomitant medications and physiotherapeutic interventions
- Clinical laboratory testing including chemistry, hematology, coagulation, and urinalysis
- Vital signs
- Physical examinations
- ECG
- ECHO: ejection fraction (EF) and fractional shortening (FS)

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[redacted]

7.3.4. Pharmacokinetic Endpoints (Treated Group only)

Standard PK parameters for eteplirsen will be estimated based on sparse sampling. The effects of demographic characteristics, concomitant medications, laboratory values, and other covariates on eteplirsen PK will be evaluated.

7.4. Discussion of Study Design

7.4.1. Choice of Study Population and Control Group

The treated group will consist of boys 7 to 16 years of age, inclusive, with a confirmed DMD diagnosis who have an out-of-frame deletion(s) that may be treated by exon 51 skipping. These are the patients for whom eteplirsen is potentially effective and may result in slowing their disease progression. Because the primary analysis will be performed on patients with a Baseline 6MWT distance of 300 to 450 meters (i.e., the group most likely to decline during the study period), approximately 70 patients with this 6MWT distance will be enrolled into the treated group and approximately 20 patients in the untreated control groups. Patients who meet all of the other entry criteria and have a 6MWT distance >450 meters may also be enrolled into the treated or untreated control groups, depending upon their DMD genotype. According to natural

history data, these patients are not expected to decline considerably over the study period; therefore they will not be included in the primary analysis (McDonald 2010a, Mazzone 2011, McDonald 2010b, McDonald 2013).

The untreated control group will consist of boys 7 to 16 years of age, inclusive, with a confirmed DMD diagnosis who have an out-of-frame deletion(s) that is not amenable to treatment by exon 51 skipping. This patient group will also have deletions in the spectrin-like repeating units, which are expressed in a similar phenotype with regards to disease manifestations and rate of progression; this group therefore serves as an appropriate control group for this study (Magri 2010). In addition, the entry criteria for both groups, with the exception of the genotype, will be identical to allow for valid comparison between the treated and untreated control cohorts. If less than 80% of the planned subjects are enrolled in the untreated control cohort, the control group may be augmented as described in Section 13.2.

7.4.2. Length of Study

Clinical studies with eteplirsen have shown the drug to be safe and well tolerated at weekly doses of up to 50 mg/kg for over 120 weeks. Study 4658-301 is designed to include efficacy assessments to Week 96. Previous clinical trial data demonstrated that treatment with eteplirsen for more than 32 to 36 weeks was a sufficient time to see a significant discernible difference in the 6MWT and in the percentage of dystrophin positive-fibers. Patients will continue to receive weekly doses of eteplirsen and participate in safety follow-up assessments through Week 96. Treated patients may also participate in the safety extension (not to exceed 48 weeks) as defined in the schedule of events in Table 4.

7.4.3. Choice of Efficacy Measurements

The 6MWT was selected as the primary efficacy endpoint as it is the most reliable and sensitive instrument currently available to demonstrate a functional change for DMD patients (McDonald 2010c). The 6MWT is a frequently used measure of functional capacity in regards to both strength and endurance, and has already been validated in pediatric populations in which normative data are available. It has been used as a primary outcome measure to support the registration of treatments for other neuromuscular disorders. Specific to DMD, the 6MWT is being used as a primary endpoint in clinical trials with ambulatory DMD patients not only to evaluate eteplirsen, but also other disease modifying drugs such as ataluren and drisapersen. As loss of ambulation is considered an important milestone in the progression of DMD, it is being measured as a secondary endpoint using the 6MWT.

The dystrophin protein levels (quantified by Western blot) and dystrophin intensity levels determined by immunofluorescence were selected as secondary efficacy endpoints since the very low levels of dystrophin in these patients represent the hallmark of the DMD disease, and eteplirsen has been shown to increase such levels significantly.

The ability to rise independently is increasingly recognized as an important functional ability for DMD patients, as being able to rise independently allows patients to move about independently, without the fear of not being able to get up if they should fall. Thus, the NSAA total and subscores were selected as highly relevant endpoints for DMD patients.

8. PATIENT POPULATION AND SELECTION

8.1. Inclusion Criteria

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

1. Be a male with DMD and meet one of the following criteria:
   - Have an out-of-frame deletion that may be treated by exon 51 skipping (e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63). These patients will be enrolled into the treated group.
   - Have an out-of-frame deletion that is not amenable to treatment by exon 51 skipping but is amenable to treatment by skipping other exons (i.e., whole exon deletions in which the reading frame may be restored by skipping 1 or 2 exons). These patients will be enrolled into the untreated control group.
2. Be 7 to 16 years of age, inclusive.
3. Have stable pulmonary function (FVC% of predicted ≥50% and not require nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Have intact right and left bicep muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Have been on a stable dose of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: patients may be allowed to take other (non-RNA antisense or non-gene therapy) medication including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β-blockers, potassium, and coenzyme Q, provided they have been on a stable dose for 24 weeks prior to Week 1 and the dose is expected to remain constant throughout the study.
6. Achieve a mean distance of 2 separate assessments on 2 consecutive days at the Screening and Baseline visits (prior to Week 1) ≥300 meters on the 6MWT with the 2 consecutive means being within 15% of each other, and with the Screening and Baseline 6MWT conducted 3 to 5 weeks apart. Personal assistance or use of any assistive devices for ambulation is not permitted during the 6MWT.
7. Male patients who are in the treated group and are post-pubertal and sexually active must agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g., oral contraceptives).
8. Have a parent(s) or legal guardian(s) who is able to understand and comply with all the study requirements.

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

8.2. Exclusion Criteria

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

1. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks of Week 1 that may have an effect on muscle strength or function (e.g., growth hormone, anabolic steroids).
2. Previous treatment with ezutromid (BMN 195/SMT C1100) at any time.
3. Previous treatment with drisapersen (PRO051) therapy within the last 3 months. To be eligible for the study, patients who were previously treated with drisapersen must be free of any of the following prior to Week 1: a) any active skin lesions related to drisapersen injection; b) renal signs/symptoms (including proteinuria or elevated creatinine/ cystatin C); c) the presence of anti-platelet antibodies (to be tested at screening for patients who were previously treated with drisapersen); and d) abnormal platelet count.
4. Previous treatment with any other RNA antisense agent or any gene therapy within the last 6 months, or participation in any other DMD interventional clinical study within 12 weeks of Week 1, or use of the shock training system or "STS," or planned use during this study. Concurrent enrollment in any natural history, observational, or biomarker clinical trial is permitted provided the patient's participation in the other trial does not affect any of the assessments performed in the 4658-301 clinical study. For patients in the untreated control group only, continuation in an interventional trial with standard-of-care medication may also be permitted if the patient's participation in the standard-of-care interventional trial does not affect any of the assessments performed in Study 4658-301, and the patient meets all the protocol-required entry criteria.
5. Major surgery within 3 months of Week 1, or planned surgery for any time during this study, except for protocol-specified surgeries, as applicable.
6. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease, or malignancy.
7. Use of any aminoglycoside antibiotic within 12 weeks of Week 1 or need for use of an aminoglycoside antibiotic or statin during the study.
8. Have a left ventricular ejection fraction (LVEF) of <50% based on the screening ECHO or QT interval corrected by Fridericia's correction (QTcF) ≥450 msec based on the screening ECG.
9. Loss of ≥30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (i.e., fixed plantar flexion of 10 degrees or more).

10. Change in contracture treatment such as serial casting, contracture control devices, night splints, stretching exercises (passive, active, self) within 3 months prior to enrollment, or expected need for such intervention during the study.
11. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, patients who seem unwilling to comply with the study procedures, in the Investigator's opinion, are to be excluded.

8.3. Completion of a Patient's Participation in the Study and Overall Study Completion

The length of a patient's participation will be from the time the informed consent form is signed until completion of the Week 96 assessments. Following the Week 96 visit, patients in the treated group may continue in a safety extension, not to exceed 48 weeks, until the product is commercially available or until they can transition into a separate eteplirsen study.

8.4. Patient Withdrawal From the Study

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

- The patient was erroneously included in the study (i.e., was found to 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.

Patients who complete Baseline assessments and who are withdrawn from the study more than 4 weeks after a Functional Assessment visit (Week 12, 24, 36, 48 or 72) will be asked to complete all Early Termination (Week 96) assessments as soon as possible after withdrawal, and patients in the treated group will be asked to complete an End of Study visit (to complete the Week 148 assessments) within 4 weeks of their last infusion. Patients who withdraw during the Safety Extension Period (Weeks 97-148) in order to transition onto commercial drug do not need to complete the End of Study visit assessments.

9. TREATMENTS

9.1. Investigational Drug Product

Eteplirsen injection is intended for IV infusion.

9.2. Packaging and Labeling

Eteplirsen injection will be supplied as a sterile, isotonic, clear, colorless phosphate buffered saline solution with no preservatives at a concentration of 50 mg/mL in single-use vials containing a nominal volume of 2 mL or 10 mL.

The label text for the IP will comply with current Good Manufacturing Practice (cGMP) and other applicable regulatory requirements, and will minimally include the contents of the vial, the appropriate cautionary statements per 21 Code of Federal Regulations (CFR) 312.6, lot number (or alternative code), storage conditions, and the name of the Sponsor.

9.2.1. Receipt of Investigational Product

A proof of receipt, which details the quantity and description of the IP, will accompany the shipment from the Sponsor or designee to the Investigator. Details for IP receipt, storage, and dispensation recordkeeping are located in the study specific Pharmacy Manual. The Investigator must ensure that the IP is maintained in a controlled location, with limited access and temperature monitoring under appropriate storage conditions.

9.2.2. Storage

Vials of IP must be stored at a consistent temperature from 2°C to 8°C in a secured, limited-access area with temperature recording, controls, and monitoring. Details for preparation of the diluted IP for administration can be found in the study specific Pharmacy Manual.

9.3. Treatments Administered

Eligible patients who have an out-of-frame deletion that may be treated by skipping exon 51 will receive 30 mg/kg/week eteplirsen as an IV infusion for up to 96 weeks (treated group). Eligible patients who have out-of-frame deletions that are not amenable to treatment by skipping exon 51 will remain on their existing standard of care but will not receive eteplirsen throughout the study (untreated control group).

For the treated group, the following guidelines for the timing of dosing should be followed throughout the study:

1. Patients should receive eteplirsen once every 7 days starting on Study Day 1. A window of ±3 days from the scheduled dose is acceptable after the first infusion. For visits where safety assessments are not being collected, optional in-home administration of eteplirsen by a visiting nurse may be available after Week 25. For in-home dosing, additional instructions will be provided in a separate manual to the visiting nurse.

2. Patients may not receive 2 separate doses of eteplirsen within the same 60-hour period.
3. The medical monitor should be contacted in the event of a missed dose.

9.3.1. Disposition of Unused Investigational Drug Product

All unused IP vials must be maintained under adequate storage conditions in a limited-access area until time of use. Upon completion of the study, any remaining unused IP vials will be returned to the Sponsor or destroyed per the site-specific standard operating procedures to minimize the potential for contamination. Final drug accountability will be monitored by the Sponsor or its representative.

9.3.2. Administration of the Investigational Product

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

Eteplirsen will be administered as an IV infusion over a period of approximately 35 to 60 minutes. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5%, or LMX4 cream) be applied to the infusion site prior to each administration of eteplirsen.

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

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

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

9.4. Dosing Considerations

9.4.1. Dose Modification, Reduction, or Delay

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

9.4.2. Treatment Discontinuation

The Investigator or study staff will document the reason(s) for treatment discontinuation on the case report form (CRF). The following may be justifiable reasons for the Investigator or Sponsor to discontinue a patient from treatment:

- The patient was erroneously included in the study (i.e. 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 that would interfere with the assessments in Study 4658-301.

Patients who receive at least one (1) dose of IP and who are withdrawn from treatment within 4 weeks after a Functional Assessment visit (Week 12, 24, 36, 48, or 72) will be asked to return for an End of Study visit (to complete the Week 148 assessments) within 4 weeks from their last infusion. Patients who receive at least one (1) dose of IP who are withdrawn from treatment more than 4 weeks after a Functional Assessment visit (Week 12, 24, 36, 48, or 72) will be asked to complete all Early Termination (Week 96) assessments as soon as possible after withdrawal and to complete an End of Study visit (to complete the Week 148 assessments) within 4 weeks after their last infusion. Patients who withdraw during the Safety Extension Period (Weeks 97-148) in order to transition onto commercial drug do not need to complete the End of Study visit assessments.

9.5. Method of Assigning Patients to Treatment

Enrolled patients who have an out-of-frame deletion that may be treated by exon 51 skipping (e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63) will be assigned to the treated group and will receive eteplirsen 30 mg/kg/week.

Enrolled patients who have an out-of-frame deletion that is not amenable to treatment by exon 51 skipping but is amenable to treatment by skipping other exons (i.e., whole exon deletions in which the reading frame may be restored by skipping 1 or 2 exons) will be assigned to the untreated control group.

9.6. Blinding and Randomization

This is an open-label study, and therefore patients and Investigators will be aware of the patient's treatment. However, to minimize assessment bias, every effort will be made to keep the clinical evaluators unaware of the treatment group of the patients, and all biological efficacy endpoint evaluations will be performed by blinded assessors.

9.6.1. Maintaining the Blind for Clinical Evaluators

Clinical evaluators will be instructed on how to maintain blinding to treatment group as well as possible through training. Specifically, the clinical evaluators will:

- Not be involved in any aspect of care for the patients over the course of the study and will not have access to any clinical patient records including laboratory values, genetic analyses, or study-specific assessment and treatment schedules.
- Not have contact with the parents or caregivers of the patients.
- Avoid conversation with the patients about treatment, other assessments including muscle biopsies, and any other disease related topics.

- Strive to keep the conversation with patients to the necessary minimum to allow for optimal clinical assessments while keeping the topic relevant to the current evaluation.

Patients will be requested not to discuss their study treatment with the clinical evaluators.

In order to maintain the study blind, interaction between parents and clinical evaluators will be minimized. Parents of study participants will therefore be requested not to interact with clinical evaluators and will be asked to not publicly discuss their child's participation in this study. It will also be explained to parents that they will not receive any information on the clinical efficacy evaluation until the study is complete.

9.6.2. Laboratory Assessments

All laboratory assessments, notably IHC, CCI , and Western blot assays will be performed so that the raters are unaware of the time point at which the sample has been taken. A detailed description of these procedures can be found in the Laboratory Manual.

9.6.3. Randomization for Muscle Biopsy Schedule (Treated Group Only)

Upon qualification for the study during the Baseline visit, patients in the treated group will undergo muscle biopsy, and will be randomized to a second muscle biopsy schedule at Week 24 (20%), Week 48 (40%), Week 72 (20%), or Week 96 (20%). Patients in the untreated control group will not undergo muscle biopsy at any time point.

9.7. Prior and Concomitant Medications and Therapeutic Procedures

For both treatment groups, the dosing regimen for oral corticosteroids for treatment of DMD including, but not limited to, prednisolone, prednisone, or deflazacort, should be kept the same throughout the study except for modifications to accommodate changes in weight.

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

- Oral ACE inhibitors, including but not limited to perindopril and lisinopril
- Oral β-blockers, including but not limited to carvedilol and atenolol
- Angiotensin-receptor blockers, including but not limited to losartan, irbesartan, valsartan, and candesartan
- Oral laxatives, including but not limited to lactulose, Senokot, and Movicol
- Vitamin D and calcium supplements
- Alendronate (Fosamax) or other bisphosphonates used to treat osteoporosis/osteopenia by inhibiting osteoclasts

- Over-the-counter herbal preparations, including herbal supplements, vitamins, minerals, and homeopathic preparations, provided the patient had been on stable doses for 24 weeks before enrollment in this study

Recommendations for selection of medications and interventions during anesthesia include:

- The use of depolarizing muscle relaxants such as succinylcholine are not permitted in any case due to their potential to induce rhabdomyolysis in patients with DMD
- Volatile anesthetics should be avoided if possible, also due to a risk of rhabdomyolysis

Other concomitant medications (e.g., vitamins or other non-RNA antisense medications) may also be taken if, in the opinion of the Investigator, they do not interfere with study assessments and outcomes. Every attempt should be made to keep the dosage constant throughout the study treatment period (i.e., through Week 96).

Introduction of new physiotherapy interventions during the course of the study must be avoided unless the best interests of the patient are at risk. Should a contracture develop during the course of the study, and it is considered in the best interest of the patient to treat the contracture, then any of the following interventions may be used to reduce the contracture, but they must be clearly documented:

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

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

- Systemic or oral steroids for non-DMD conditions, except for treatment of an acute condition (e.g., poison ivy)
- Investigational agents for the treatment of DMD
- Any medication with the potential to affect muscle mass, strength, and/or function, such as, but not limited to, growth hormone and phosphodiesterase type 5 inhibitors
- Immunosuppressants (other than oral or systemic corticosteroids)
- Aminoglycoside antibiotic or statin (unless discussed and agreed upon with the Investigator and Medical Monitor)

9.8. Treatment Compliance

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

10. STUDY ASSESSMENTS

10.1. Study Schedule of Events

Schedules outlining the study assessments and times of assessments are shown in Section 2. Written informed consent from the parent/legal guardian(s) and assent from the patient (if applicable) to participate in this study must be obtained prior to beginning any of the procedures for Study 4658-301 (see Section 14.3 for further details).

10.2. Study Assessments by Visit

Assessments of AEs and concomitant medications will be performed at every study visit. Various study assessments may be performed at different sites.

A 'Local Site' will be the site a patient most frequently visits for infusions and routine assessments. All assessments scheduled on the same day as eteplirsen administration are to be completed prior to initiation of eteplirsen infusion, except for postdose blood draws for PK as indicated in Section 2.

A 'Hub Site' will perform functional efficacy and cardiac assessments. Patients enrolled at certain Local Sites will therefore need to travel to a Hub Site. A Hub Site may also be a particular patient's Local Site. Hub Sites have been introduced to minimize the number of clinical evaluators and thereby reduce rater-dependent variability in the study cohort. Each Hub Site will have at least 2 expert clinical evaluators who will have undergone standardized training and have been certified to be capable of performing all clinical assessments as specified for this study. To further reduce variability, every effort should be made to have each patient assessed by the same clinical evaluator for each specific assessment throughout the entire study; all assessments will be done in the same order as listed in the Clinical Evaluator Manual, at approximately the same time of day, and clinical evaluators will not have access to prior test results or information related to study-specific or routine patient care. Efficacy evaluations will be performed in the morning and cardiac assessments will be performed after completion of the functional assessments, at a consistent time of day for each visit during the course of the study.

CCI [redacted]

To reduce the burden on the untreated control patients, all protocol-specified assessments after Week 12 may be performed at the Hub Site (Table 5). If a patient transfers to their assigned Hub Site for collection of safety assessments (e.g., laboratory assessments, vital signs, and physical examinations), the functional assessments must be done first, and the safety assessments should be done after completion of the functional assessments.

A 'Surgical Unit' will perform study-specific muscle biopsy procedures. Muscle biopsies for all treated patients will be performed at only 2 surgical sites, and all muscle biopsy tissue preparation including sectioning will be performed at a single central pathology laboratory according to a predefined protocol to reduce potential bias. Patients enrolled at certain Local Sites will need to travel to one of the 2 surgical sites for the biopsy procedures. A Surgical Unit may also be a particular patient's Local and/or Hub Site. However, personnel performing 'Hub'

and 'Surgical' functions will be clearly separated from those performing 'Local' functions and will not have access to any information related to routine care or treatment of the patient.

10.2.1. Screening Period (Up to 10 weeks prior to Week 1)

If a patient has not previously been genotyped, the screening informed consent form (ICF) and genotyping should be the only procedures done until the genotype results are known. For these patients, the time interval for the screening period begins when the genotype results are received; therefore the screening period may be longer than 10 weeks for these patients.

At Local Sites:

- Screening Informed Consent – Overall study requirements and details surrounding Screening and Baseline assessments for the treated and untreated control groups
- Assess eligibility, including collection of a blood sample to determine/confirm genotype
- Medical history, including treatment history
- Full physical examination, including examination of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- [redacted] CCI [redacted]
- Height

At Hub Sites (Screening Functional Assessment Visit):

The Screening period may require a 2-night overnight stay near the Hub Site. Assessments will begin in the mornings on Day 1 and Day 2 in the order described in the Clinical Evaluator Manual.

Day 1:

- Informed Consent– Overall study requirements and details surrounding Screening and Baseline assessments for the treated and untreated control groups
- Assess eligibility
- [redacted] CCI [redacted]
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT)

Day 2:

- CCI [redacted]
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT)

Either Day 1 or Day 2:

- ECG
- ECHO

10.2.2. Baseline Period (3-5 Weeks after Screening Functional Assessment Visit)

The muscle biopsy should be the last Baseline procedure performed.

At Hub Sites (Baseline Functional Assessment Visit; occurs within 4 weeks prior to Week 1):

The Baseline period may require a 2-night overnight stay near the Hub Site. Assessments will begin in the mornings on Day 1 and Day 2 in the order described in the Clinical Evaluator Manual.

Day 1:

- Assess eligibility
- Vital signs
- Height and ulnar length
- CCI [redacted]
- [redacted]
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT.)
- NSAA
- CCI [redacted]
- [redacted]

Day 2:

- CCI [redacted] P
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT.)
- NSAA
- CCI [redacted]
- [redacted]

Either Day 1 or Day 2:

- ECG

At Surgical Units (After eligibility has been confirmed) (for the treated group only):

The muscle biopsy should be the last Baseline procedure performed after the Local Site has confirmed eligibility. Assessments at the Surgical Unit should be performed in the order described in the Clinical Evaluator Manual.

- Informed Consent
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity
- Blood sample for biomarkers of DMD disease progression, CCI [redacted]
- A muscle biopsy will be performed on all patients in the treated group. The biopsy may be obtained as soon as eligibility is confirmed (i.e., Baseline assessment is complete and genotype is confirmed), prior to the first dose of eteplirsen. The first dose of eteplirsen must be within 4 weeks of the Baseline Functional Assessment visit. Surgery must be performed within the 4-week window between the Baseline Functional Assessment visit and Week 1. Patients in the treated group may not begin to receive eteplirsen until after the Baseline muscle biopsy has been performed.

10.2.3. Weekly Infusions (Weeks 1-96) (for the treated group only)

At Local Sites:

- Vital signs, including include blood pressure, heart rate, respiration, and oral temperature. Vital signs will be measured 30 minutes prior to the start of the infusion and 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be reduced to pre-infusion and 30 minutes after the end of the infusion. Vital signs should be collected as close to or at the exact indicated times as possible.
- Eteplirsen will be administered via an IV infusion. Patients should be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (e.g., lidocaine 2.5%, prilocaine 2.5% or LMX4 cream) be applied prior to infusions. Refer to the Pharmacy Manual for specific instructions regarding IP reconstitution with normal saline.

10.2.4. Additional Procedures for Week 1

The assessments below should occur during a single day at a patient's Local Site.

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight (This measurement will be used to calculate the eteplirsen dose for patients in the treated group.)
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity
- Blood sample for biomarkers of DMD disease progression, CCI [redacted]
- At a subset of sites for patients in the treated group, 1 blood sample for assessing plasma drug concentrations (PK) will be taken within 2 hours prior to the start of the first infusion of eteplirsen.

10.2.5. Additional Procedures for Week 4

Assessments should occur during a single day at the patient's Local Site.

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity
- Blood sample for biomarkers of DMD disease progression, CCI [redacted]

10.2.6. Additional Procedures for Week 8

Assessments should occur during a single day at the patient's Local Site.

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs

- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity
- At a subset of sites for patients in the treated group, blood samples for assessing plasma drug concentrations (PK) will be obtained 5 to 10 minutes after completion of drug administration. PK samples will also be taken approximately 1-2 hours after completion of drug administration.

10.2.7. Additional Procedures for Weeks 12, 24, 36, 48, and 72 (Functional Assessment Visits)

At Local Sites:

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity
- At Week 24 and Week 48: Serum sample for biomarkers of DMD disease progression, CCI [redacted]
- At Week 24: At a subset of sites for patients in the treated group, blood samples for assessing plasma drug concentrations (PK) will be obtained 5 to 10 minutes after completion of drug administration. PK samples will also be taken approximately 1-2 hours after completion of drug administration.
- At Week 48: At a subset of sites for patients in the treated group, PK blood samples will be obtained within 2 hours prior to the start of the infusion, at the end of the infusion prior to flushing the infusion line, and 5 to 10 minutes after completion of the infusion. PK samples will also be taken approximately 1-2 hours and 2-4 hours after completion of drug administration.
- At Week 72: At a subset of sites for patients in the treated group, blood samples for assessing plasma drug concentrations (PK) will be obtained 5 to 10 minutes after completion of drug administration. PK samples will also be taken approximately 2-4 hours after completion of drug administration.

At Hub Sites:

The Functional Assessments may require a 2-night overnight stay near the Hub Site. Assessments will begin in the mornings on Day 1 and Day 2 in the order described in the Clinical Evaluator Manual.

Day 1:

- Height and ulnar length

CCI [redacted]

- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT.)
- NSAA

CCI [redacted]

Day 2:

- CCI [redacted]
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT.)
- NSAA
- CCI [redacted]
- [redacted]

Either Day 1 or Day 2:

- ECG
- ECHO (Week 24 only)

At Surgical Units: Week 24, 48, or 72 only (for the treated group only):

- Depending upon randomization, patients in the treated group may have a muscle biopsy performed following the Week 24, 48, 72, or 96 (Section 10.2.10 for Week 96 procedures) infusion and functional assessments. The biopsies must occur within 2 weeks after the specified visit, after the clinical evaluation, and at least 48 hours after the most recent infusion.

10.2.8. Additional Procedures for Weeks 16, 32, 40, 44, 60, 84 (for the treated group only)

At Local Sites:

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin

- Vital signs
- Weight
- At Week 16 and Week 32: At a subset of sites for patients in the treated group, blood samples for assessing plasma drug concentrations (PK) will be obtained 5 to 10 minutes after completion of drug administration.
- At Week 40, Week 60, and Week 84: At a subset of sites for patients in the treated group, PK blood samples will be obtained within 2 hours prior to the start of the infusion and 5 to 10 minutes after completion of the infusion. PK samples will also be taken approximately 1-2 hours and 2-4 hours after completion of drug administration.

10.2.9. Additional Procedures for Weeks 20, 28, 44, 52, 56, 64, 68, 76, 80, 88, 92 (for the treated group only)

At Local Sites:

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight

10.2.10. Additional Procedures for Week 96 (or Early Termination Visit, if more than 4 weeks after a Functional Assessment Visit)

At Local Sites:

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity
- Serum sample for biomarkers of DMD disease progression, CCI [redacted]
- At a subset of sites for patients in the treated group, blood samples for assessing plasma drug concentrations (PK) will be obtained within 2 hours prior to the start of the infusion, at the end of the infusion prior to flushing the infusion line, and 5 to 10 minutes after completion of the infusion. PK samples will also be taken approximately 1-2 hours and 2-4 hours after completion of drug administration.

At Hub Sites:

The Functional Assessments may require a 2-night overnight stay near the Hub Site. Assessments will begin in the mornings on Day 1 and Day 2 in the order described in the Clinical Evaluator Manual.

Day 1:

- Height and ulnar length
- CCI [redacted]
- CCI [redacted]
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT.)
- NSAA
- CCI [redacted]
- [redacted]

Day 2:

- CCI [redacted]
- 6MWT (Pulse will be recorded immediately prior to and after the 6MWT.)
- NSAA
- CCI [redacted]
- [redacted]

Either Day 1 or Day 2:

- ECG
- ECHO

At Surgical Units: Week 96 only (for the treated group only):

- Depending upon randomization, patients in the treated group may have a muscle biopsy performed following the Week 96 infusion and functional assessments. The biopsies must occur within 2 weeks after the specified visit, after the clinical evaluation, and at least 48 hours after the most recent infusion.

10.2.11. Safety Extension (Not to Exceed 48 Weeks)

Patients in the treated group may continue on in the safety extension for a period not to exceed 48 weeks, until the product is commercially available or until they can transition into a separate eteplirsen study.

During the safety extension, patients will continue to receive 30 mg/kg/week eteplirsen as an IV infusion, and will undergo physical examinations and assessments of safety laboratory parameters, weight, AEs and concomitant medications as specified in Table 4.

10.2.12. Week 148 (End of Study Visit)

Assessments should occur during a single day at the patient's Local Site.

- Full physical examination including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Immunogenicity

10.3. Efficacy Assessments

The efficacy assessments performed during this study are briefly summarized below. Detailed instructions for performing these assessments are provided in the Clinical Evaluator's Manual. Every effort will be made to ensure that the clinical evaluator (rater) remains blinded to the patient's treatment group (treated/untreated control).

10.3.1. Primary Efficacy Assessment: 6-Minute Walk Test

The 6MWT will be performed by standardized procedures for all patients as outlined in Section 2. The patient will be asked to walk a set course of 25 meters for 6 minutes (timed), and the distance walked (in meters) will be recorded.

The same evaluator will complete the assessments on each patient throughout the study and at the same approximate time in the morning (which will be noted). The 6MWT will be performed on 2 consecutive days.

10.3.2. Secondary Efficacy Assessment

10.3.2.1. Muscle Biopsy (Treated Group Only)

Upon qualification for the study during the Baseline visit, patients in the treated group will undergo muscle biopsy and will be randomized to a second muscle biopsy schedule at Week 24 (20%), Week 48 (40%), Week 72 (20%), or Week 96 (20%).

Biopsies at Weeks 24, 48, 72, and 96 must be taken:

- Within 2 weeks after the specified visit;
- After the clinical evaluation; and

- At least 48 hours after the most recent infusion.

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

Muscle biopsy samples will be collected at the Surgical Units and will be sent to a central laboratory for analysis. All analyses related to quantification of the dystrophin protein will be performed by personnel blinded to the time point of the patient's muscle biopsy (i.e., pre- and post-treatment). Details are provided in the Laboratory Manual.

Additional assessments completed on the muscle biopsy samples are presented in Section 10.3.3.6.

10.3.2.2. North Star Ambulatory Assessment (NSAA)

The NSAA will be performed for patients in both the treated and untreated control groups at the time points specified in Section 2. The NSAA is a clinician-administered scale that rates patient performance on various functional activities (Mazzone 2010). During this assessment, patients will be asked to perform 17 different functional activities, including a 10 meter walk/run, rising from a sit to stand, standing on one leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. Patients will be graded as follows: 2 = normal, no obvious modification of activity; 1 = modified method but achieves goal independent of physical assistance from another; and 0 = unable to achieve goal independently. The NSAA will be performed on 2 consecutive days.

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10.4. Safety Assessments

Safety will be assessed for all enrolled patients from the time the informed consent is signed through the End of Study visit or Early Termination visit. In the event of an early termination, a follow-up assessment will occur 4 weeks after the last infusion for patients in the treated group (see Section 9.4.2). Safety parameters will include ECG, ECHO, physical examinations, vital signs, clinical laboratory testing (hematology, chemistry, and urinalysis), the use of concomitant medications and physiotherapeutic interventions, and collection of AEs. The patient's Local Site Investigator will be responsible for communicating any potentially significant ongoing AEs that may interfere with the functional assessments at the Hub Site. The Hub Site and Surgical Unit Investigators are responsible for communication of any AEs that occur at the Hub Site or Surgical Unit, respectively, to the Local Site Investigator for follow-up.

10.4.1. Physical Examination

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

10.4.2. Vital Signs, Weight and Height

Vital signs (blood pressure, heart rate, respiration, and oral temperature), height, and weight will be measured at the time points specified in Section 2. Clinically significant changes will be documented in the patient source records. All assessments will be performed after patients have remained seated for 5 minutes. Pulse rate and respiratory rate should be measured over 1 minute.

Ulnar measurements will be recorded for all patients at each Hub Site visit. Height should be measured with shoes off. If standing height cannot be obtained, height should be calculated using the following equation (Gauld 2004):

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

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

10.4.3. Clinical Laboratory Tests

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

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

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

- Values have reached normal range and/or Baseline levels; or
- In the judgment of the Investigator together with the Sponsor's Medical Monitor, abnormal values assessed to be not related to the administration of test article or other protocol-specific procedures, and additional assessments are not medically indicated.

10.4.4. Electrocardiogram

A 12-lead ECG will be obtained at the time points specified in Section 2. ECGs will be performed only after the patient is in the supine position, resting, and quiet for a minimum of 15 minutes. The ECG will be manually reviewed and interpreted by medically qualified personnel using a central vendor according to pre-specified criteria. The Investigator will review the results of the centrally read ECG report and designate the findings as normal, abnormal (CS or NCS).

10.4.5. Echocardiogram

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in Section 2. The ECHO will be reviewed and interpreted by medically qualified personnel using a central vendor according to pre-specified criteria. Ejection fraction (EF) and FS will be noted. The Investigator will review the results of the ECHO report and designate the findings as normal, abnormal (CS or NCS).

10.4.6. Concomitant Medications and Therapies

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

10.4.7. Adverse Events

The collection of adverse events is described in Section 11.

10.5. Pharmacokinetic Assessments (Only at a Subset of Sites for Patients in the Treated Group)

Blood samples for assessing plasma drug concentrations will be obtained at a subset of sites from at least 24 patients in the treated group at the visits and time points specified in Section 2. Refer to the Laboratory Manual for the study for sample processing. Plasma samples will be analyzed to determine concentrations of eteplirsen.

11. ADVERSE EVENTS

11.1. Collection of Adverse Events

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

All AEs from the time of informed consent through the End of Study visit (or early termination from the study) will be recorded in each individual patient's CRF. For patients who prematurely discontinue the study (see Section 9.4.2), AEs will continue to be recorded until 4 weeks after the last eteplirsen infusion for the randomized group or through the Early Termination visit for the untreated control group.

If, at any time after the patient has completed participation in the study (see Section 9.4.2), the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly/probably or definitely related to the IP (Section 11.3.1) or is possibly/probably or definitely related to a study procedure (Section 11.3.2), then the event and any known details must be reported promptly to the Sponsor.

11.2. Definition of Adverse Events

11.2.1. Adverse Event (AE)

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

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

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

11.2.2. Serious Adverse Event (SAE)

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

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

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

11.3. Classification of Adverse Events

Each AE whether serious or 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:	The event is clearly not related to the IP
Possibly/probably related:	The event could be related/is likely to be related to the IP
Definitely related:	The event is clearly related to the IP

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

11.3.2. Relationship to Study Procedures

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

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

11.3.3. Relationship to Underlying Disease

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

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

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

11.3.4. Severity of Adverse Events

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

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

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

11.3.5. Outcome

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

11.3.6. Action Taken Regarding the Investigational Drug Product

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

11.3.7. Expectedness of an Adverse Event

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

11.3.8. Suspected Unexpected Serious Adverse Reactions (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) will be handled by appropriate personnel at the Sponsor or designee and reported within the required timelines in an unblinded fashion to regulatory authorities and institutional review boards/independent ethics committees

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

11.4. Recording Adverse Events

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

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

11.5. Reporting Serious Adverse Events

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

11.6. Special Situations

11.6.1. Overdose

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

11.6.2. Death

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

11.6.3. Responsibilities of the Investigator

- The responsibilities of the Investigator and his or her staff include 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 SAE 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

11.6.4. Responsibilities of the Sponsor

The responsibilities of the study Sponsor (Sarepta Therapeutics, Inc.) include 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
- Ensuring accurate recording of AEs and SAEs
- Notification of expedited SAEs to sites
- Annual safety reporting to regulatory authorities and IRBs/IECs according to regional requirements

12. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

12.1. Recording of Data

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

12.2. Quality Assurance

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

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

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

12.3. Retention of Study Documents

At study completion, all CRF data for an individual site will be copied onto a compact disc (CD) and provided to the Investigator for retention in the Study Files. The supporting Site Study Files must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved for such indication, until 2 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.

12.4. Termination of Study or Study Site

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, 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
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements consistent with 21 CFR 312 or the European Clinical Trial Directive 2001/20/EC

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

13. STATISTICAL METHODS AND PLANNED ANALYSES

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 final Statistical Analysis Plan (SAP) for this study.

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

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

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

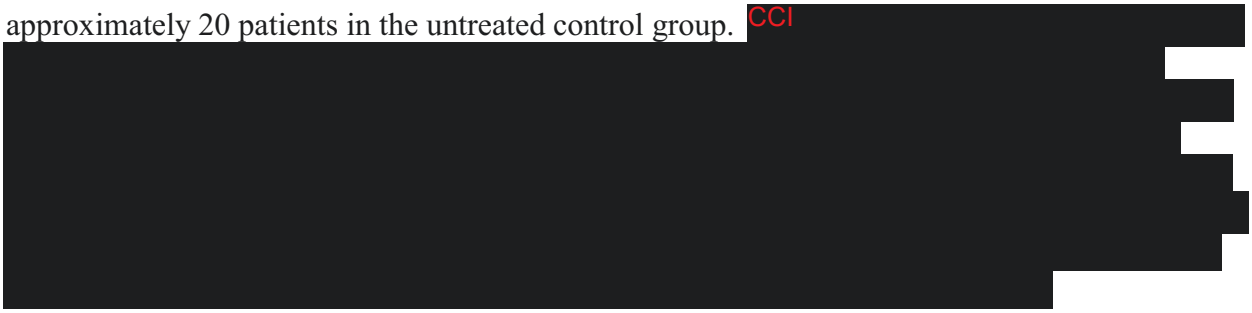
Endpoints will be assessed primarily using simple descriptive statistics and/or inferential statistics. Baseline will generally be defined for the treated group as the last available value before dosing, and the equivalent time point for the untreated control group.

13.2. Determination of Sample Size

DMD patients have consistently shown progressive decline in 6MWT data secondary to disease progression. The extent of decline has been shown to be affected by stride length and age (McDonald 2010a), and the use of steroids (Mazzone 2011). For example, in a natural history study that included patients with a broader range of ages and functional abilities, patients who were older than 7 years of age lost a mean of 42.3 meters (SD = 73.9 meters; N = 71) over the course of a year (Mazzone 2011). In another natural history study of 18 boys with Duchenne/Becker muscular dystrophy 4 to 12 years of age, patients lost a mean of 57 meters (SD =104 meters) over the course of approximately 1 year (McDonald 2010b); the distance lost was even greater (115 meters) in boys older than 7 years of age (n = 10). More recently, completed studies with the drug ataluren from PTC Therapeutics presented a decline of about 60 meters after 48 weeks in the 34 placebo-treated patients who were ≥7 years old who were on steroid for the duration of the study (McDonald 2013).

This study will enroll approximately 90 patients with Baseline 6MWT distance of 300 to 450 meters, including approximately 70 patients in the eteplirsen-treated group and

approximately 20 patients in the untreated control group. CCI



Additionally, approximately 20 patients (10 treated vs 10 untreated control) with Baseline 6MWT distance of >450 meters at Baseline will be enrolled.

13.3. Analysis Sets

Patients will be analyzed by treatment (eteplirsen 30 mg/kg/week versus untreated control). Three analysis populations will be considered:

Efficacy Set: All patients in treated and untreated control groups who have at least 1 post-Baseline functional assessment. The efficacy set for the primary efficacy analyses will be patients with baseline 6MWT distance of 300 to 450 meters, inclusive. If external control patients are included as a comparator of eteplirsen-treated group, the efficacy set may be expanded accordingly, with the primary efficacy set for the primary endpoint defined in the SAP.

Safety Set: Treated patients who are enrolled in the study and receive at least 1 dose of eteplirsen and untreated control patients who are enrolled in the study and have at least 1 post-Baseline safety assessment.

Pharmacokinetic Set: All patients in treated group who receive a full dose of IP at the visits where PK sampling is to be done and for whom there are adequate PK samples from which to estimate population PK parameters.

13.4. Protocol Deviations

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

13.5. Disposition, Demographics, and Baseline Characteristics

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

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

13.6. Prior and Concomitant Medications and Physiotherapeutic Interventions

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

13.7. Medical History

Medical history will be presented in data listings.

13.8. Dosing and Compliance

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

13.9. Efficacy Analyses

All efficacy data will be summarized descriptively by visit and treatment group. Actual values and change from Baseline values will be summarized by time point and treatment.

The efficacy set for the primary efficacy analysis will be patients with a Baseline 6MWT distance of 300 to 450 meters, inclusive.

13.9.1. Efficacy Variables

13.9.1.1. Primary Efficacy Endpoint

- Change from Baseline to Week 96 in the 6MWT

13.9.1.2. Secondary Efficacy Endpoints

- Change from Baseline in dystrophin protein levels quantified by Western blot (treated patients only)
- Change from Baseline in dystrophin intensity levels determined by immunofluorescence (treated patients only)
- Ability to rise independently from the floor (without external support), as indicated by an NSAA subscore of "2" (without modification) or "1" (Gower's maneuver)
- Loss of ambulation (to be defined in the SAP),
- Change from Baseline in FVC % predicted
- Change from Baseline in NSAA total score

13.9.2. Analyses of Primary Efficacy Endpoint

The analysis of change from Baseline to Week 96 (the primary time point of interest) in the 6MWT will be based on a mixed model repeated measures (MMRM) analysis, with treatment group, time, time by treatment group interaction, Baseline 6MWT distance, and Baseline 6MWT distance by time interaction as fixed effects; and patient as a random effect. Additional baseline variables may be added as covariates in the SAP. A heterogeneous autoregressive (1) variance-covariance matrix will be used. Estimates for changes from Baseline at each time point in each treatment group and for treatment differences will be provided with 95% confidence intervals and descriptive p-values using appropriate contrasts from the model. Due to the potential difference in progression based on DMD genotype in the control group, notably those with deletions amenable to skipping exon 44, additional sensitivity analyses may be performed.

If there is strong evidence suggesting that data for any of these endpoints deviate from normal distribution, then an analysis of covariance (ANCOVA) for ranked data (Stokes 2000) will be utilized.

13.9.3. Analyses of Secondary Efficacy Endpoints

As muscle biopsies will be confined to the treated group, the analysis of the secondary endpoints of change from Baseline in the dystrophin protein levels by Western blot and dystrophin intensity levels determined by immunofluorescence will be based on a 1-sample permutation t-test. These analyses will be performed for patients in the treated group only.

The analysis of the secondary endpoints of time from Baseline to loss of the ability to rise independently (from supine to standing) and time to loss of ambulation will be analyzed using the Kaplan-Meier method. The analyses of the secondary efficacy endpoints of change from baseline in FVC% predicted and change from baseline in NSAA total score will be similar to the primary endpoint.

13.10. Safety Analyses

13.10.1. Safety Variables

The safety and tolerability of eteplirsen will be evaluated by:

- The type, frequency, severity, timing, and relationship to IP of AEs, SAEs, and AEs leading to discontinuation. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by primary system organ class (SOC) and preferred term (PT)
- Adverse events will be classified as treatment-emergent (TEAE) and non-emergent. TEAEs are those AEs that develop or worsen during the on-treatment period. An AE will be considered treatment emergent if it begins on or after dosing with IP and up until 30 days after the last administration of IP. Non-emergent events are those that develop during the pre-treatment period

- Clinical laboratory testing including chemistry, hematology, coagulation, and urinalysis
- Vital signs
- Physical examinations
- ECG
- ECHO: EF and FS

13.10.2. Safety Analysis

Safety analyses will be descriptive in nature. When appropriate, patients who have been treated previously with drisapersen will be summarized separately within the treatment group. 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.

13.10.2.1. Adverse Events

For treated patients, only TEAEs will be summarized. Non-treatment emergent events will be recorded in data listings. For all AE tables, the number and percent of patients reporting AEs (grouped by MedDRA SOC and PT) will be summarized by treatment group. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

As untreated patients (control group) will have no TEAEs, AEs collected post-qualification for the study will be summarized similarly to treated patients' TEAEs. All captured AEs for this control group will be listed.

Multiple occurrences of the same AE (at the PT level) in the same patient will be counted only once in frequency tables. If a patient experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship and maximum severity to IP will be used to summarize AEs by relationship and severity. Treatment-related TEAEs will be defined as those that the Investigator considers possibly/probably or definitely related to the IP.

The following summary tables will be produced:

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

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

The following listings will be produced:

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

13.10.2.2. Physical Examination and Vital Signs

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

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

13.10.2.3. Clinical Laboratory Tests

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

13.10.2.4. Electrocardiograms

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

13.10.2.5. Echocardiograms

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

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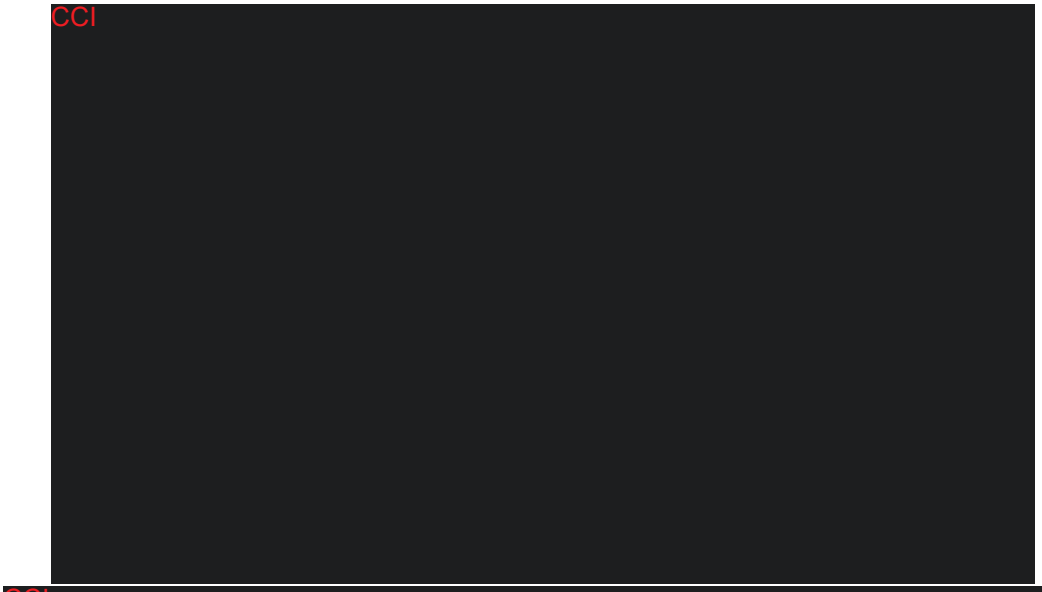

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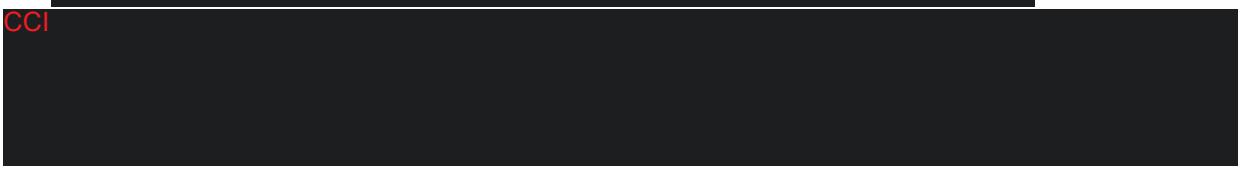

13.12. PK Analysis

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

PK analysis of plasma concentration-time data of eteplirsen will be performed using nonlinear mixed-effects modeling. For population PK analyses, data from this study may be combined with those of other studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, concomitant medications, etc.) will be tested as potential covariates affecting PK parameters. A separate population PK analysis plan will outline the methodology that will be utilized in developing an exposure-response model that would take into account the disease natural progression and the available eteplirsen concentration data to relate its exposure with the change in disease progression.

13.13. Interim Analyses

An interim analysis will be performed after approximately 35 patients with baseline 6MWT between 300 and 450 meters, inclusive, have completed their Week 96 assessments. Given the small size of the untreated control group, external control patients, including those amenable to exon 51 skipping, may be identified and compared to the eteplirsen-treated group. The details of the interim analysis will be specified in a SAP before the database lock for the interim analysis.

13.14. Other Statistical Issues

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

14. SPECIAL REQUIREMENTS AND PROCEDURES

14.1. Compliance with Ethical and Regulatory Guidelines

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

14.2. Institutional and Ethics Review

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

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

Written informed consent from each patient's parent(s) or legal guardian(s) and written assent from each patient, if applicable, must be obtained at the Local Site, Hub Site, and Surgical Unit (if applicable) before any study-specific screening or Baseline period evaluations are performed at these respective study sites. In addition, each patient's parent/guardian must sign a Study Consent form (Treated or Untreated Control) at their Local Site Day 1 visit, prior to any Day 1 study procedures being performed. In addition, if the patient's local site is different from their Hub Site, the patient's parent/guardian must re-consent at their Hub Site with the appropriate Study Consent form at their Week 12 Functional Assessment visit, prior to any Week 12 study procedures being performed. For patients enrolled prior to implementation of Amendment 2 of the protocol, the patient's parent/guardian must re-consent (at both the local site, and Hub Site if different from the local site) as soon as possible after implementation of Amendment 2 for the patient to continue in the study beyond Week 48. Patients enrolled prior to implementation of protocol Amendment 2 must re-consent at the surgical unit if they are scheduled for biopsy at Week 72 or Week 96. For each of these consent processes, written assent from each patient, if applicable, must also be obtained in addition to the written informed consent by the parent/guardian. One copy of the signed informed consent/assent documents will be given to the patient; the Investigator will retain the original copies of these documents.

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

consent and additional elements, as applicable, as specified in the 21 CFR 50.25 and the European Clinical Trial Directive 2001/20/EC.

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 Anonymity

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

15. STUDY DOCUMENTATION AND GENERAL INFORMATION

15.1. Essential Study Documents

The following documentation will be collected prior to study enrollment:

- Signed Form FDA 1572, or equivalent
- Curriculum vitae for each person on the Form FDA 1572 or equivalent
- Signed Financial Disclosure Forms for each person listed on the Form FDA 1572 or equivalent
- IRB/IEC approval for all study materials (ICF, Protocol, any recruitment materials, etc.) and IRB/IEC membership list
- Clinical laboratory normal ranges, when appropriate
- Clinical laboratory licenses (CAP/CLIA or other)
- Signed final protocol page
- IB acknowledgement
- A blank copy of the IRB-/IEC-approved informed consent (and assent documents, if applicable) and authorization
- A fully executed Clinical Trial Agreement and Confidentiality Agreement

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

The study site files will also contain, patient accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB/IEC correspondence, deviations, biological sample records, and SAE and IND safety reports / Safety Alert Letters.

15.2. General Information

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

15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics Inc. However, at the conclusion of this clinical study, a clinical study report will be

prepared. In addition, a manuscript will be prepared for publication in a reputable scientific journal under the direction of the Sponsor. Sarepta Therapeutics Inc., will publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by Sarepta Therapeutics Inc., as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov. After completion of the study, results will be disseminated through ClinicalTrials.gov.

15.4. Product Handling and Complaints Reporting

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

16. REFERENCES

American Academy of Orthopaedic Surgeons (AAOS). http://www.aaos.org/research/outcomes.outcomes_peds.asp. Website accessed on: 26 Jul 2013.

AAOS. http://www.aaos/org/ Website accessed on: February 2014.

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.

Amor CJ, Spaeth MC, Chafey DH, Gogola GR. Use of the Pediatric Outcomes Data Collection Instrument to evaluate functional outcomes in arthrogryposis. J Pediatr Orthop. 2011 Apr-May;31(3):293-6.

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

CCI [redacted]

CDC-MMWR. Prevalence of Duchenne/Becker Muscular Dystrophy Among Males Aged 5-24 Years – Four States, 2007. 2009;1119-22.

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. Neuromuscul Disord. 2002;12(10):926-9.

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

Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. Dev Med Child Neurol. 2004;46:475-80.

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.

CCI [redacted]

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

Magri F, Govoni, A, et al. Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up. J. Neuro. 2011;258:1610-23.

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. Neurol. 2011;77(3):250-6.

Mazzone E, Martinelli D, Berardinelli A, Messina S, D'Amico A, Vasco G et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2010 Nov;20(11):712-6.

McDonald CM, Henricson EK, Abersch RT, et al. The 6-minute walk test and other endpoints in Duchenne Muscular Dystrophin: Longitudinal natural history observations over 48 weeks from a multicenter study. Muscle and Nerve. 2010a Sep;48(3):343-56.

McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test in Duchenne/Becker muscular dystrophy: Longitudinal Observations. Muscle Nerve. 2010b Apr 41:500-10.

McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, Elfring GL, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve. 2010c Apr;41(4):500-10.

McDonald CM, Henricson EK, Abresch RT, Florence J, Eagle M, Gappmaier E, et al. The 6-minute walk test and other clinical endpoints in Duchenne muscular dystrophy: Reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve. 2013;48:357-68.

CCI [redacted]

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

Stokes ME, Davis CS, Koch GG. Categorical data analysis using SAS® system, 2nd Edition. SAS Publishing, 2000.

Uzark K, King E, Cripe L, Spicer R, Sage J, Kinnett K, et al. Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. Pediatrics. 2012;130:e1559-66.