STATISTICAL ANALYSIS PLAN

Protocol 4658-203

An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-Stage Duchenne Muscular Dystrophy

(Protocol version: Amendment 2, 08 June 2017)

Version: 1.0

Date: 11 February 2019

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

SIGNATURE PAGE

Prepared by:

PPD PPD

PPD , MS, PPD Date
PPD

Reviewed by:

PPD PPD

PPD PhD, PPD PPD Date
PPD

Approved by:

PPD PPD

PPD MD Date
PPD PPD
P
P

PPD PPD

PPD MD, MS Date
PPD PPD
PPD

PPD PPD

PPD PhD Date
PPD PPD
P
P
D

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Expanded Term
AE	adverse event
AUC	Area under the plasma concentration-curve
CDISC	Clinical Data Interchange Standards Consortium
Cmax	Maximum plasma concentration
CL	Total clearance
CLR	Renal clearance
CSR	Clinical Study Report
DMD	Duchenne muscular dystrophy
eCRF	electronic case report form
ECG	electrocardiogram
ECHO	echocardiogram/echocardiography
IHC	immunofluorescence histochemistry
LLOQ	Lower Limit of Quantitation
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	[redacted]
[redacted]	[redacted]
MRT	mean residence time
CCI [redacted]	[redacted]
PK	pharmacokinetics
CCI [redacted]	[redacted]
PT	Preferred term
QTcF	QT interval corrected by the Fridericia Correction Formula
CCI [redacted]	[redacted]
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	standard MedDRA queries
SOC	System organ class
t½	Elimination half-life
TEAE	Treatment emergent adverse event

Tmax	Time to maximum plasma concentration
Vss	Apparent volume of distribution at steady state
WHO Drug	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a detailed description of the statistical methods and procedures that will be used to analyze and report results for Study 4658-203, titled "An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-Stage Duchenne Muscular Dystrophy".

This SAP has been prepared based on Protocol Amendment 2, dated 08 June 2017.

2. STUDY OBJECTIVES

2.1. Primary Objectives

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

2.2. Secondary Objectives

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

[redacted] CCI [redacted]

[redacted].

2.4. Pharmacokinetic Objectives

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

3. STUDY DESCRIPTION

3.1. Study Overview

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

Patients will be evaluated for inclusion during a Screening/Baseline period of up to 5 weeks. Eligible patients for the eteplirsen-treated group will receive once weekly IV infusions of 30 mg/kg eteplirsen for up to 96 weeks. An extension period may be considered prior to the end of the 96-week planned dosing period. Eligible patients for the untreated group (e.g., deletions of exons 44, 45, or 53) will not receive treatment of eteplirsen. Untreated patients will undergo select safety, functional, and laboratory assessments but will not provide blood samples for PK determination or undergo muscle biopsy procedures.

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

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

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

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

3.1.1 Randomization of Muscle Biopsy Schedule

All eteplirsen-treated patients will have a muscle biopsy performed at Baseline. Additionally, eteplirsen-treated patients will be randomly assigned 1:1 through interactive response technology (IRT) to a second muscle biopsy to be performed at Week 48 or 96. Untreated patients will not have muscle biopsies performed.

3.1.2 Blinding

The evaluation of the quantification of the dystrophin protein from muscle biopsies will be performed by personnel blinded to the time point of the patient's muscle biopsy (i.e., pre- and on-treatment).

In order to avoid bias, clinical evaluators performing functional assessments (e.g., CCI) will be blinded to study treatment, will not be involved in the clinical care of patients, and will not access any clinical or safety related patient information.

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

3.2. Study Endpoints and Other Variables

3.2.1 Safety Endpoints

The following endpoints will be accessed for all patients in the study:

- Incidence of adverse events
- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations
- Incidence of abnormalities on ECGs and ECHOs

3.2.2 Secondary Endpoints

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

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

CCI

3.2.4 Pharmacokinetic Endpoints

The following PK parameters will be determined, as appropriate for eteplirsen-treated patients only:

- Maximum plasma concentration (Cmax)
- Time to maximum plasma concentration (tmax)
- Area under the plasma concentration-curve (AUC)
- Apparent volume of distribution at steady state (Vss)
- Elimination half-life (t½)
- Total clearance (CL)
- Mean residence time (MRT)
- Renal clearance (CLR)

3.3. Sample Size and Power

Sample size for this study is based upon qualitative considerations; no formal sample size calculations will be performed. Up to 40 patients will be included in this study: approximately 20 patients in the eteplirsen-treated group (those amenable to exon 51 skipping) and up to 20 in the untreated control group (those not amenable to exon 51 skipping).

3.4. Planned Analyses

3.4.1 Periodic Safety Data Reviews

Periodic safety analyses will be performed for Investigator's Brochure (IB) update, and regulatory submissions (Development Safety Update Report [DSURs]) as necessary. These periodic safety analyses will continue to be performed approximately every 12 months during this study.

3.4.2 Final Analysis

A final analysis of safety and efficacy will be conducted once the last patient completes or discontinues the entire study and the resulting database is cleaned, quality assured, and locked. All statistical analyses will be performed by or under the supervision of the Sponsor.

All available data will be included in data listings and tabulations.

Because the untreated control group had not been able to enroll the planned number (20) of patients, had a high dropout rate, and resulted in a very small sample size, an external control dataset may be identified and used to evaluate the effect of eteplirsen treatment. The statistical methods for the identification and use of the external control dataset may be presented in a separate SAP if deemed appropriate. The results from analysis of

eteplirsen treated patients as compared to an external control if performed will not be included in the Clinical Study Report (CSR), but may be reported in a standalone report.

4. GENERAL STATISTICAL METHODS AND CONVENTIONS

4.1. General Methods

Summary statistics will be presented by treatment group, unless stated otherwise. Treatment group refers to patients receiving eteplirsen and patients in the untreated group.

For continuous variables, descriptive statistics will include the number of patients with data to be summarized (n), mean, standard deviation, median, minimum, and maximum.

For categorical/qualitative variables, descriptive statistics will include frequency counts and percentages. The total number of patients in a treatment group will be used as the denominator for percentage calculations, unless stated otherwise.

4.2. Handling of Missing Data

4.2.1 Imputation of Missing Values

4.2.2 Handling of Incomplete Dates

All available data will be included in data listings and tabulations.

An incomplete date will occur when the exact date an event occurred or ended cannot be obtained for a patient. Incomplete dates will be imputed as described below. No other imputation of missing data will be performed.

- For a partial or missing medication date, the medication will be classified as a concomitant medication unless the available part of the date indicates it is impossible for the drug to be concomitant. For example, if only the year for the

stop date is available and the year is prior to the year of dosing, the medication will be classified as a prior medication.

- For a partial AE onset date, the event will be classified as treatment emergent if the month and/or year of the onset date are on or after the initiation of eteplirsen for eteplirsen treated patients or after Day 1 for untreated patients and within 28 days of the last dose of eteplirsen for eteplirsen treated patients or within a day after last visit for untreated patients, or if the month and/or year of the onset date are on or after the date of the qualifying visit for untreated patients. All AEs with a missing AE onset date will be classified as treatment emergent.
- For the purpose of calculating the time since DMD diagnosis or duration of prior corticosteroid use, if the date of DMD diagnosis or the start date of corticosteroid use has a missing day but known month and year, then the 15th of the month will be used in the calculation. If the date has a missing day and month and only the year is known, December 31st of the recorded year will be used in the calculation.

In all cases, the original missing or incomplete dates will be presented in the data listings.

4.3. Analysis Populations

There will be 3 analysis populations with the definitions below for analyzing safety data, efficacy data, biopsy data and pharmacokinetics, as appropriate.

- **Full Set:** Full set includes all patients who are enrolled in the eteplirsen group and receive at least 1 dose of eteplirsen as well as all patients who are enrolled in the untreated group who have at least 1 assessment post-enrollment assessment. Full Set will be used for summarizing safety and efficacy data.
- **Muscle Biopsy Set**: This set includes all patients who receive at least one dose of eteplirsen and who have data from both Baseline (pre-treatment) and Week 48 or Week 96 (on-treatment) muscle biopsy samples.
- **Pharmacokinetic Set:** All patients who receive at least one dose of eteplirsen and for whom there are adequate PK samples with which to estimate PK parameters. The PK Set will be further described in a separate PK SAP.

4.4. Multiple Testing and Comparisons

No adjustment will be made for the testing of multiple endpoints.

4.5. Adjustment for Covariates

Not applicable.

4.6. Subgroups

Due to small sample size, no subgroups will be identified for this study.

4.7. Presentation Over Time

For endpoints that are collected serially over time, assessments/test values will be assigned to a specific timepoint (e.g., study week) based upon the electronic case report form (eCRF) page on which the assessments/test values were reported.

For an efficacy endpoint, an unscheduled/early termination assessment may be used in the summary by timepoint if the unscheduled assessment was within 2 weeks of a missing scheduled assessment. If unscheduled assessments are collected with multiple dates or times within a given visit, the result closest to the scheduled visit date will be used for summary presentations. If 2 measurements have the same distance to the expected date, the earlier assessment value will be used.

For safety endpoints, unscheduled assessments will not be included in the summary by timepoint.

4.8. Algorithm, Computation and Definition of Derived Variables

Day 1

For eteplirsen treated patients, Day 1 will be defined as the date of the first eteplirsen administration. For untreated patients, Day 1 will be defined as the date of the last Screening/Week 1 assessment.

Study Day

Study day will be defined as Event Date – Day 1 + 1, if Event Date is on or after Day 1; otherwise, as Event Date – Day 1, if Event Date precedes Day 1.

Duration on Study

Duration on study will be calculated as the duration in weeks from Day 1 to the date of study completion/discontinuation as recorded on the END OF STUDY eCRF (if completed) or the date of the last study assessment or procedure. The duration in weeks calculated above will then be categorized to one of the following intervals: < 24, 24 to < 48, 48 to < 72, 72 to 96, ≥ 96.

Duration of Treatment

For treated patients, duration of eteplirsen treatment will be calculated as the duration in weeks from the date of first dose of eteplirsen to the date of the last eteplirsen administration as recorded on the STUDY DRUG ADMINISTRATION eCRF plus 7 days (or 1 week), i.e., (Last dose date - first dose date + 7)/7. The duration in weeks calculated above will then be categorized to one of the following intervals: < 24, 24 to < 48, 48 to < 72, and ≥ 72.

Baseline

For treated patients, baseline will be defined as the last value prior to the first dose of eteplirsen administration. For untreated patients, baseline will be defined as the last value on or before the Day 1 date.

CCI [redacted]

CCI

CCI

Planned Dose and Overdose

The body weight-based planned dose was calculated based on most recent weight of previous visits. When calculating the planned dose, the body weight is rounded to single decimal using conventional rounding rules. While in preparing actual dose, an unconventional rule is applied for calculating the volume of the concentrated drug (50 mg/ml) in milliliter. Any volume number 0.1 or above is rounded up, e.g. 25.14 ml is rounded up to 26 ml, and any volume number below 0.1 is rounded down, e.g. 25.09 ml is round up to 25 ml. The overdose is defined as any actual dose >10% above the planned body weight-based dose.

Treatment-emergent Adverse Event (TEAE)

For treated patients, an AE will be considered treatment-emergent if it starts in the time period starting with the initiation of the first dose of eteplirsen and ending 28 days after the last dose of eteplirsen. For untreated patients, an AE will be considered treatment-emergent if it starts on or after the Day 1 date.

Treatment-related Adverse Event

A treatment-related AE is any AE reported on the ADVERSE EVENTS eCRF that is marked as definitely related, or probably/possibly related to study drug.

Treatment Emergent Laboratory Abnormality

For treated patients, a treatment-emergent laboratory abnormality will be defined as any laboratory abnormality occurring or worsening after the initiation of eteplirsen dosing and within 28 days of the last dose of eteplirsen. For untreated patients, a treatment-emergent laboratory abnormality will be defined as any laboratory abnormality occurring or worsening on or after the Week 1/Screening assessment.

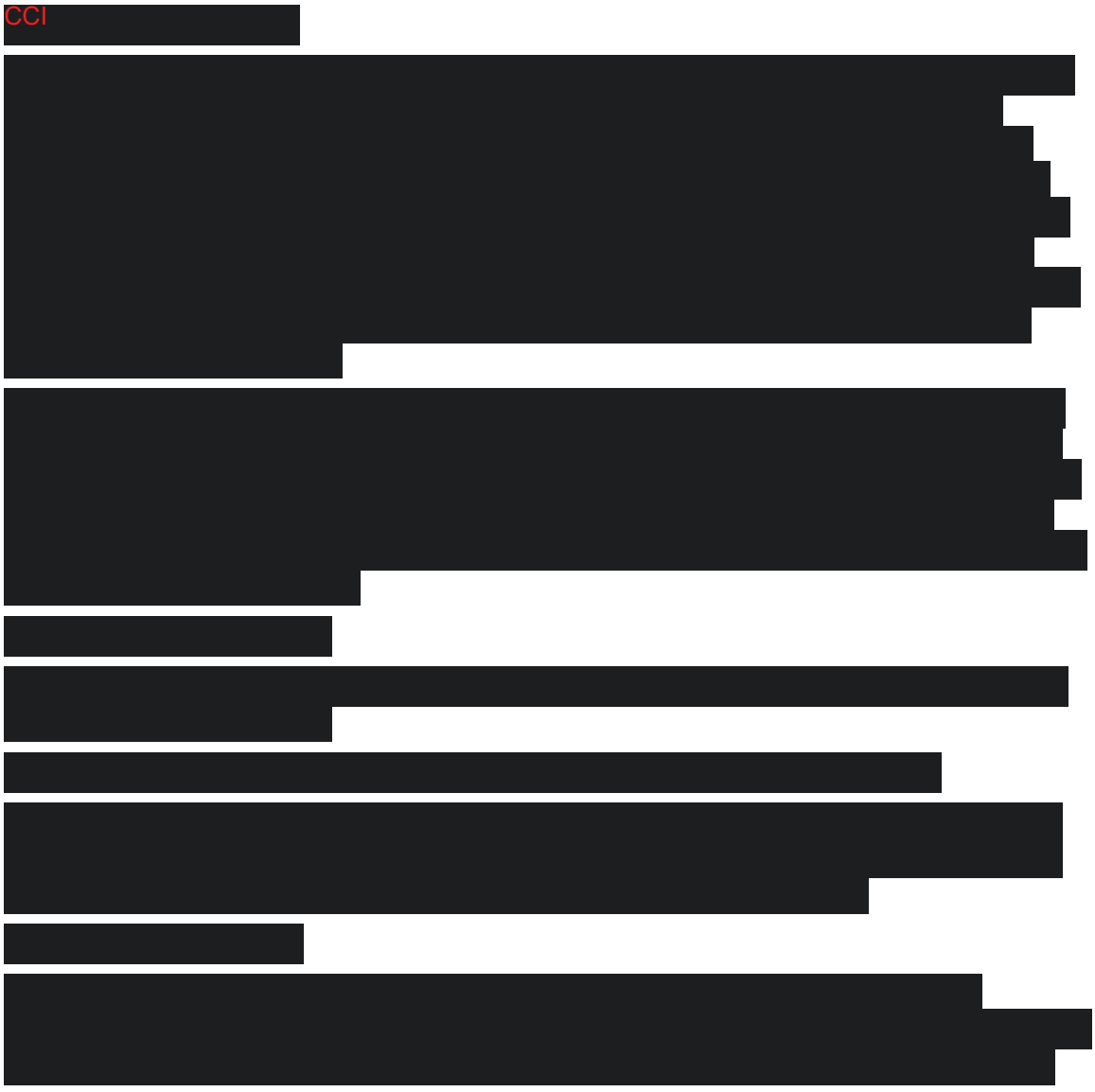
Prior Medication

A prior medication will be any medication taken and completed prior to the first dose of eteplirsen for treated patients or on or before the Day 1 date for untreated patients.

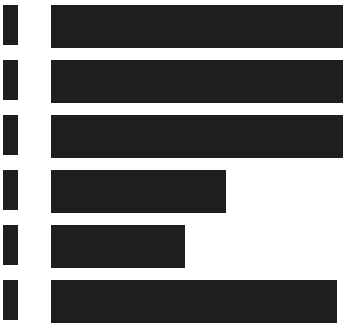
Concomitant Medication

A concomitant medication will be any medication that is taken in the time period starting with the initiation of the first dose of eteplirsen and ending 28 days after the last dose of eteplirsen for treated patients or on or after the Day 1 date for untreated patients.

CCI



CCI



4.9. Programming Conventions

This section details general conventions to be used for the production of tables, figures and listings. Departures from these general conventions will be specified in appropriate sections.

- For continuous or quantitative variables, mean and median values will be formatted to 1 more decimal place than the measured value on the eCRF. Standard deviation and standard error values will be formatted to 2 more decimal places than the measured value on the eCRF. Minimum and maximum values will be presented with the same number of decimal places as the measured value on the eCRF. Percentages will be presented with 1 decimal place.
- For categorical variables, the number and percentage of a category will be presented in the form XX (YY%), where the percentage is YY.
- Percentages of patients with laboratory toxicities will be based on nonmissing values unless stated otherwise.
- Study Day will appear in the data listings as appropriate.
- Date variables will be formatted as DDMMMYYYY for presentation.
- SAS® Version 9.4 or higher will be the statistical software package used for all analyses unless otherwise specified.
- The Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Implementation Guide (ADaMIG) V1.0 for preparing data sets will be used for this study.
- The CDISC Study Data Tabulation Model Implementation Guide (SDTMIG) V3.2 for preparing data sets will be used for this study.
- Tables, figures, and listings will be presented in landscape orientation.
- Listings will be sorted by treatment, patient and then assessment or event start date unless otherwise specified.

5. STATISTICAL ANALYSES

5.1. Patient Disposition

The number of patients enrolled, the number in the safety population, the number randomized to muscle biopsy, the duration of the study (weeks) [both continuous and categorical interval summaries], the number and percentage of patients completing the study through Week 96 (i.e., completers), and the number and percentage of patients prematurely discontinuing before Week 96 will be summarized. Reasons for premature discontinuation will also be summarized. All analyses will be performed by treatment group.

Patient eligibility will be presented in a listing.

5.2. Demographics and Baseline Characteristics

Demographic characteristics including age (years), race, ethnicity, and baseline characteristics including height (cm), weight (kg), body mass index (BMI; kg/m2), time since DMD diagnosis (months) to Baseline, corticosteroid type (Deflazacort or Prednisone), corticosteroid frequency (continuous versus intermittent), mutation type(s), and duration of prior corticosteroid treatment (months) to Day 1 will be summarized by treatment group. Demographic data and baseline characteristics will also be presented in data listings.

5.3. Prior and Concomitant Medications

Concomitant medications will be coded by preferred term (PT) using the most recent World Health Organization (WHO) Drug Dictionary (WHODRUG, 01DEC2013). The number and percentage of patients in the safety population taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification, pharmacological subgroup, and WHO drug PT by treatment group. At each level of summarization, a patient is counted once if he/she reported 1 or more medications at that level.

All prior medications and concomitant medication will be presented in data listings.

5.4. Medical History

Medical history data for the safety set will be presented in data listings.

5.5. Physiotherapeutic Interventions

A listing of all physiotherapeutic interventions will be provided.

5.6. Protocol Deviations

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

5.7. Exposure to Study Drug

The total number of infusions received, cumulative amount of drug received (mg), total volume of drug administered (mL), duration on eteplirsen in 24-week intervals, and the continuous number of weeks on eteplirsen will be summarized for all eteplirsen-treated patients. Dosing information will be provided in a data listing.

A listing of patients with overdose will be generated.

5.8. Safety Analyses

Safety analyses will be descriptive in nature. Safety analyses will include summaries of the following:

- The type, frequency, severity, timing, and relationship to the investigational drug product of AEs, SAEs, and discontinuations due to AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 17.1 or higher) and will be reported by primary system organ class (SOC) and PT.
- Safety laboratory testing including hematology, coagulation, serum chemistry, and urinalysis
- Vital signs
- Physical examinations
- ECG and/or ECHO

5.8.1 Adverse Events

In general, only TEAEs will be summarized (for untreated subjects, AEs that first occur or worsen in severity after the study enrollment are considered treatment-emergent). Non-treatment-emergent adverse events will be recorded in the data listings. Unless noted otherwise, for all AE tables, the number and percentage of patients reporting AEs will be grouped using the MedDRA, SOC, and PT and summarized for treated patients, untreated patients, and overall.

An overall summary table of adverse events will be produced and will include the frequency count and percentage of patients with

- TEAE
- Treatment-related TEAE
- Severe TEAE
- Treatment-Emergent SAE
- Treatment-Emergent Related SAE
- TEAE leading to discontinuation of study drug
- TEAE leading to death

The number of events at each severity level (mild, moderate, severe) will also be included.

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 a different relationship/severity, the event with the strongest relationship or maximum severity to investigational drug product will be used to summarize AEs by relationship and severity.

The following summary tables will be produced:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- TEAE by PT in descending frequency
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT, and severity
- Treatment-related TEAEs by PT in descending frequency
- Treatment-Emergent SAEs by SOC and PT
- Treatment-related Treatment-Emergent SAEs by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- Non-serious TEAEs by SOC and PT, displaying both number of subjects and number of events

The following listings will be produced:

- All AEs
- AEs leading to treatment discontinuation
- SAEs

5.8.2 Adverse Events of Special Interest

Summaries of TEAEs of special interest will be summarized by SOC and PT. All standard MedDRA queries (SMQs based on MedDRA version 17.1) listed below will include broad and narrow terms. The AEs of special interest (AESI) are:

- Hypersensitivity (hypersensitivity SMQ)
- Renal toxicity (acute renal failure SMQ)
- Infusion-related reaction (IRR) (AEs occurring within 24 hours of the start of any infusion [including events that occurred on the same date as an infusion where infusion start time or AE onset time was not reported])

For all IRRs as defined above, adjudicated IRRs will be identified by a pharmacovigilance physician. All IRRs as defined above that are considered as related to study drug by investigators will be counted in the list of adjudicated IRRs. In addition, all

IRRs as defined above that meet the following criteria will be excluded from the list of adjudicated IRRs:

- AE was an infusion site, application site, or other local AE not associated with IRR
- AE had a clear alternate etiology that could be ascertained based on the reported event (eg, reaction to plaster, assessed as related to procedure or underlying disease by investigator)
- AE not associated with an IRR due to the nature of the event or biologically implausible (eg, fibula fracture, chalazion)

A summary table will be generated and include the following:

- Number of patients with adjudicated IRRs
- Number of adjudicated IRRs
- Number of adjudicated IRRs with event start time reported
- Number of events on any day for adjudicated IRRs

A corresponding listing will be generated for each table. Additionally, a table and listing corresponding to the AESIs that were related to study drug or moderate or severe will be produced.

An overall summary of AESI events will include the total number of events, number of serious events, number of related events, number of not related events, number of mild events, number of moderate events, number of severe events, and number of events occurring on the same day as an infusion.

5.8.3 Additional Adverse Events for Review

Summaries of Additional TEAEs for review will be summarized by SOC and PT. All SMQs based on MedDRA Version 17.1 are listed below and will include broad and narrow terms.

Additional AEs for review are:

- Drug-induced hepatotoxicities (cholestasis and jaundice of hepatic origin SMQ, hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions SMQ, hepatitis, noninfectious SMQ, liver neoplasms, benign [including cysts and polyps] SMQ, liver malignant tumors SMQ, liver tumors of unspecified malignancy SMQ, liver-related investigations, signs and symptoms SMQ, liver-related coagulation and bleeding disturbances SMQ)
- Cardiac events (cardiomyopathy SMQ, cardiac failure SMQ, and arrhythmia related investigations, sign and symptoms SMQ)
- Thrombocytopenia (hematopoietic thrombocytopenia SMQ)
- Port-related events (embolic and thrombotic events, venous SMQ, extravasation events (injections, infusions, and implants) SMQ, PTs in the following High Level Terms (HLTs): sepsis, bacteremia, viremia and fungemia NEC (not elsewhere

classified), implant and catheter site reactions, PTs in the following HLGTs: endocardial disorders, and device issues. In addition, a search will be performed on the verbatim terms for "port", "central venous" and "central line"). Note: The port-related events will only be identified for patients who have a port placed/inserted and for events that occur after the port insertion occurred. It is noted that port insertion may occur during treatment or prior to the start of treatment. Percentages will be calculated based on the total number of patients who have had a port inserted

A corresponding listing will be generated for each table. Additionally, a table and listing corresponding to the additional AEs for review that were related to study drug or moderate or severe will be produced.

An overall summary of additional AEs for review will include total number of events, number of serious events, number of related events, number of not related events, number of mild events, number of moderate events, number of severe events, and number of events occurring on the same day as an infusion.

5.8.4 Clinical Laboratory Evaluation

Clinical chemistry, hematology, coagulation, and urinalysis results will descriptively be summarized by treatment group and by selected time point. Baseline value, highest/lowest postbaseline value, and final observation and the corresponding change from Baseline will be summarized for treated patients and untreated patients. Frequency tables of patients with potentially clinically significant laboratory parameter values at any time point will be generated. The total number of potentially clinically significant values will also be summarized. Potentially clinically significant values can be found in Appendix 1 tables 1-3.

A shift table will present the number and percentage of patients in each cell resulting from cross-tabulating the status (low, normal, and high) of the highest/lowest postbaseline value versus that of the baseline for each laboratory test, if applicable, by treatment group. If a specific test can have both a significant low and high, then a shift table will be generated for each direction. The percentage will be based on the total number of patients in the Safety Set.

All patient-level clinical laboratory values will be displayed in data listings. In addition, values meeting the potentially clinically significant abnormalities criteria will be presented in data listings. Treatment-emergent abnormalities will be indicated in the listing.

5.8.5 Vital Signs and Other Physical Findings

Vital signs, height/length, and weight will be summarized by treatment group and by selected time point. Baseline value, highest/lowest postbaseline value, and final observation and the corresponding change from Baseline will be summarized for treated patients, untreated patients. Highest/lowest value is considered as the largest absolute change from Baseline for systolic blood pressure, diastolic blood pressure, and respiratory rate, and highest value for pulse rate and temperature. The highest/lowest value will not be summarized for height, weight, or ulnar length. Frequency tables of patients with potentially clinically significant vital sign values will be generated. The

total number of potentially clinically significant values will also be summarized. Potentially clinically significant values can be found in Appendix 1 Table 4.

Vital signs will be listed for all patients. In addition, values meeting the predefined markedly abnormal criteria will be presented in a data listing. Treatment-emergent abnormalities will be indicated. Height and weight will also be listed.

5.8.6 Electrocardiograms and Echocardiograms

For each ECG parameter, the Baseline value, the highest/lowest postbaseline value, final observation, and the corresponding change from Baseline will be summarized for treated patients and untreated patients. The highest/lowest ECG value is the largest change for QT Interval corrected by the Fridericia Correction Formula (QTcF), QRS and PR intervals, highest value for QT, and largest absolute change for heart rate. Frequency tables of patients with potentially clinically significant ECG values will also be generated. The total number of potentially clinically significant values will also be summarized. Potentially clinically significant values can be found in Appendix 1 Table 5.

For each ECHO parameter, including the left ventricular ejection fraction (LVEF) value, Baseline value, final observation, and the corresponding change from Baseline will be summarized for treated patients and untreated patients. Frequency tables of predefined markedly abnormal ECHO values will also be generated. Markedly abnormal values can be found in Appendix I Table 5.

All patient-level values for ECG and ECHO variables will be displayed in a data listing. In addition, values meeting the predefined markedly abnormal criteria will be presented in a data listing. Treatment-emergent abnormalities will be indicated.

5.8.7 Other Safety Assessments

All physical examination results will be listed.

5.9. Efficacy Analyses

For any efficacy assessment that is taken on 2 consecutive days within a visit (i.e., CCI), the average value will be used. If the assessment is taken only on one day, then the value on that day will be used. A value that is marked as invalid on the eCRF will be considered a missing value.

5.9.1 Analysis of Secondary Efficacy Endpoints (Muscle Biopsy-Based Endpoints)

The analyses of dystrophin protein levels determined by Western blot and dystrophin intensity in muscle biopsy tissue determined by IHC were originally described in a separate muscle biopsy-based endpoints SAP, which was approved on 14 August 2017. The muscle biopsy SAP described both interim and final analyses of biopsy endpoints. However, the interim statistical analysis of muscle biopsy-based endpoints was not performed. A revision of the original muscle biopsy SAP is warranted due to coordinated analyses of all efficacy endpoints for supporting CSR. Thus, this SAP describing statistical methods for analyses of muscle biopsy endpoints will supersede the previous

separate muscle biopsy SAP. The results of muscle biopsy endpoints will be reported separately as an addendum report to the CSR.

Correlation among different types of dystrophin related endpoints listed both in the secondary efficacy endpoints and CCI may be graphically displayed using scatter plot. The Spearman's rank correlation coefficients will be calculated if appropriate. The effect of body weight and treatment duration on the dystrophin related endpoints will also be graphically displayed using scatter plot or histogram, if deemed appropriate.

5.9.1.1. Quantity of Dystrophin Protein Expression as Measured by Western Blot

For each time point (Baseline, Week 48 or Week 96), 2 blocks of tissues will be analyzed by Western blot, each with two replicates of gels to determine the dystrophin level (% normal). The block average value from two replicate gels will be computed. The overall average is calculated as the mean of the block average values. The overall average values will be used for all analyses. In the case of only 1 available gel for a block, then that value will be used as the block average value.

For the calculation of average assay value, if there are assay results outside of the limits of quantification, different imputation methods will be used (Table 1). Values less than the lower limit of quantification (LLOQ) will be imputed using one of 3 methods: as 0, as 0.24 (level immediately below the LLOQ), and as the actual measured value. Of them, the main analysis will be based on the actual measured value. Analyses based on other imputation methods will be considered sensitivity analyses.

Table 1: Imputation Method for Values Below the Limits for Western blot

Imputation type	Treat value<=LLOQ as	Analysis type
1	As measured	Main analysis
2	0	Sensitivity analysis
3	0.24	Sensitivity analysis

Dystrophin level (% normal) determined by Western blot will be summarized for baseline and each of the on-treatment timepoints (Week 48 and 96). In addition, change in dystrophin from baseline and the fold change from baseline to each on-treatment timepoints will be summarized. Fold change will be calculated in two ways: (1) calculated for each individual as post-baseline value/ baseline value and summarized using descriptive statistics, (2) calculated as the ratio of the treatment mean value post-baseline/treatment mean value at baseline.

A one-sample permutation test will be used to test the null hypothesis that the mean change from Baseline in dystrophin level is 0. In addition, at the final analysis, a two-

sample permutation test will be used to test the null hypothesis that the mean change from Baseline to Week 96 is the same as the mean change from Baseline to Week 48.

CCI [redacted]

5.9.1.2. Change from Baseline to Week 48 and Week 96 in Dystrophin Intensity as Determined by Immunohistochemistry (IHC)

Dystrophin intensity level determined by IHC will be based on the average value for each timepoint (Baseline, Week 48, or Week 96). It will be summarized descriptively for baseline and each of the on-treatment timepoints (Week 48 and 96). In addition, change from Baseline and fold change from Baseline will be summarized descriptively. Fold change will be calculated in two ways: (1) calculated for each individual as post-baseline value/ baseline value and summarized using descriptive statistics, (2) calculated as the ratio of the treatment mean value post-baseline/treatment mean value at baseline. A one-sample permutation test will be used to test the null hypothesis that the mean change from Baseline is 0. In addition, at the final analysis, a two-sample permutation test will be used to test the null hypothesis that the mean change from Baseline to Week 96 is the same as the mean change from Baseline to Week 48.

A patient-level listing will be provided.

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

5.10. Pharmacokinetic Analyses

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

Pharmacokinetic parameters for eteplirsen will be calculated using non-compartmental analysis. Actual sampling times will be used in all final PK analyses; per protocol times will be used to calculate mean plasma concentrations for graphical displays. The PK parameters that will be determined include: Cmax, tmax, AUC, Vss, t½, CL, MRT and CLR.

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

The details of PK analyses will be described in a separate PK SAP.

6. CHANGES IN PLANNED ANALYSES

6.1. Changes from Clinical Protocol-Planned Analyses

Compared to protocol specified analyses, the changes are made as follows:

- CCI [redacted]
- CCI [redacted]
- The observed values and changes from baseline for clinical laboratory assessments, vital signs and ECG will only be summarized for baseline, the last visit (final observation) and the highest/lowest values. All clinical laboratory assessments, vital signs and ECG results by visit will be in data listing.
- The untreated patient group is intended to evaluate the natural history of the DMD disease for patients who are not amenable to exon 51 skipping and is not considered eligible as a current control group for eteplirsen treated patients due to the following: 1) only 7 patients not amenable to exon 51 skipping were enrolled as supposed to planned 20 patients in untreated group, 2) untreated patients have much less assessment frequency of adverse events during study, 3) most untreated patients have dropped out the study earlier. Thus, no direct comparison is made between eteplirsen treated patients and untreated patients. No hypothesis test, no p-value and no inferential statistics will be made for comparison of eteplirsen treated patients and untreated patients.
- Due to complexity of identifying an external control dataset, the statistical methods for the identification and use of the external control dataset will not be described in this SAP. No analysis of eteplirsen-treated patients as compared to an external control will be performed.
- If an external control is identified in the future, the analysis results may not be included in the CSR, and may be reported in a standalone report.
- CCI [redacted].
- No other changes are planned or made.

6.2. Changes from Previous Statistical Analysis Plans

Compared to previous Muscle Biopsy SAP, the changes are made as follows:

- A revision of the muscle biopsy SAP is made to integrate the analyses of muscle biopsy endpoints into this SAP as final analyses of all efficacy endpoints for supporting CSR.
- The previously planned interim analysis of muscle biopsy-based endpoints was not performed.
- Due to evaluation of analytical method for exon 51 skipping in skeletal muscles as determined by CCI, the statistical method of analyzing exon 51 skipping is revised to be the same as the methods for other biopsy based endpoints.

7. APPENDEX 1: ABNORMALITIES OF INTEREST

Appendix Table 1. Chemistry Laboratory Abnormalities of Interest

Test	Unit	Predefined Change		Markedly Abnormal Criteria
		Decrease	Increase	
BUN	mmol/L	NA	NA	Value >1.5× Baseline and >ULN
Creatinine	µmol/L	NA	35	Value > ULN
Sodium	mmol/L	8	8	NA
Potassium	mmol/L	1.1	1.0	Value >5.5 mmol/L or <3 mmol/L
Chloride	mmol/L	9	8	NA
Uric acid	µmol/L	NA	NA	>1×ULN
Calcium	mmol/L	0.30	0.30	NA
AST (SGOT)	U/L	NA	NA	Value ≥2× Baseline Value and >ULN
ALT (SGPT)	U/L	NA	NA	Value ≥2× Baseline Value and >ULN
Gamma glutamyltransferase	U/L	NA	NA	Value >3× Baseline Value and > ULN
Alkaline phosphatase	U/L	NA	NA	Value >1.5 × ULN
Albumin	g/L	10	10	< LLN or >ULN
Total bilirubin	µmol/L	NA	10	Value >1.5× ULN
Lactate dehydrogenase	U/L	NA	NA	Value ≥2× Baseline Value
Creatine phosphokinase	U/L	NA	NA	Value ≥2× Baseline Value
Cystatin C	mg/L	NA	NA	>ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LLN = lower limit of normal; NA = Not Applicable; ULN = upper limit of normal

Appendix Table 2. Hematology Laboratory Abnormalities of Interest

Test	Unit	Markedly Abnormal Criteria
Hematocrit	1	<LLN
Hemoglobin	g/L (or mmol/L)	<LLN
Red blood cell count	trillion/L	<LLN
White blood cell count	10^p/L	>1.5 × ULN or <LLN
Platelet count	10^9/L	<150 or <200 with a decrease of at least 100
Basophils (abs)	10^9/L	>ULN or <LLN
Eosinophils (abs)	10^9/L	>1.5 × ULN or <LLN
Lymphocytes (abs)	10^9/L	<LLN
Monocytes (abs)	10^9/L	<LLN
Neutrophils (abs)	10^9/L	>1.5 × ULN or <0.000001

abs = absolute; LLN = lower limit of normal; ULN = upper limit of normal

Appendix Table 3. Urinalysis Laboratory Abnormalities of Interest

Test	Markedly Abnormal Criteria
Protein in urine	> 1+
Blood in urine	Positive (+)
RBCs in urine	>0

Appendix Table 4. Vital Sign Abnormalities of Interest

Variable	Units	Markedly Abnormal Criteria Lower limit	Markedly Abnormal Criteria Upper limit
Systolic blood pressure	mmHg	<90	>140
Diastolic blood pressure	mmHg	<40	>90
Pulse rate	beats/minute	<60	>130
Respiratory rate	breaths/min	<12	>20
Temperature	°C	<36.0	>38.0
Weight	kg	Decrease of 7% or more	NA

NA = not applicable

Appendix Table 5. Electrocardiogram and Echocardiogram Abnormalities of Interest

Variable	Units	LLN	ULN	Age Group (years)	Markedly Abnormal Criteria
Heart rate	Beats per minute	60	130		NA
QTcF interval	msec	NA	NA	All	Screening Visit >450
				<12	>480
				≥12	>500
				All	<320 Increase >60 >450 >480 >500
QRS interval	msec	NA	NA	<12	IVCD or any QRS conduction disturbance with a QRS >110 msec
				≥12	IVCD or any QRS conduction disturbance with a QRS >120msec
PR interval	msec	NA	NA	<12	>190
				≥12	>220
Left ventricular ejection fraction	%	NA	NA	All	<55%
Fractional shortening	%	NA	NA	All	<29%

IVCD = intraventricular conduction delay; LLN = lower limit of normal; NA = not applicable; QTcF= QT interval Fridericia corrected; ULN = upper limit of normal

CCI

CCI

CCI

CCI

CCI

CCI