STATISTICAL ANALYSIS PLAN

Protocol 4658-301 (PROMOVI)

An Open-Label, Multicenter, Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy

(Protocol Version 5 [Amendment 4], 02 Jun 2017)

Type of Analysis Plan:	Final Analysis
Version:	Final 1.2
Date:	5 Aug 2019
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Expanded Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
DMD	Duchenne muscular dystrophy
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
FVC	forced vital capacity
CCI	[redacted]
IRR	infusion-related reaction
KIM-1	kidney injury molecule-1
KM	Kaplan-Meier
LLN	lower limit of normal
LLOQ	lower limit of quantification
LOD	limit of detection
LOA	loss of ambulation
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
[redacted]	[redacted]
CCI	[redacted]
CCI	[redacted]
NSAA	North Star Ambulatory Assessment
CCI	[redacted]
CCI	[redacted]
PK	pharmacokinetic

PMO	phosphorodiamidate morpholino oligomer
CCI	[redacted]
PT	Preferred Term
QTcF	QT interval corrected by Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQs	Standardised Medical Dictionary for Regulatory Activities Queries
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
6MWT	6-minute walk test

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a detailed description of the statistical methods for the final analysis of the Sarepta Therapeutics Study 4658-301, titled "An Open-Label, Multicenter, Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy."

This SAP is based on protocol version 5 (Amendment 4), dated 02 Jun 2017.

2. STUDY 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 baseline 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 by the difference in change from Baseline in forced vital capacity (FVC) % predicted [redacted] 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.

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

3. STUDY ENDPOINTS AND OTHER VARIABLES

3.1. Efficacy Endpoints

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

The secondary efficacy endpoints are:

- Change from Baseline in dystrophin protein levels quantified by Western blot in eteplirsen-treated patients
- Change from Baseline in dystrophin intensity levels determined by immunofluorescence in eteplirsen-treated patients
- Ability to rise independently from the floor (without external support)
- Loss of ambulation (LOA)
- Change from Baseline in FVC % predicted
- Change from Baseline in North Star Ambulatory Assessment (NSAA) total score

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[redacted]

3.2. Safety Endpoints

The following safety endpoints will be summarized:

- Incidence, type, frequency, severity, and relationship to study drug of treatment-emergent adverse events (TEAE), serious adverse events (SAE), adverse events of special interest (AESIs), and adverse events (AEs) leading to discontinuation
- Concomitant medications and physiotherapeutic interventions

- Incidence of clinical laboratory abnormalities including chemistry, hematology, coagulation, and urinalysis
- Incidence of abnormalities in vital signs and physical examinations
- Incidence of abnormalities on electrocardiogram (ECG) and echocardiogram (ECHO): ejection fraction and fractional shortening

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3.4. Pharmacokinetic Endpoints (Eteplirsen-treated Patients Only)

PK concentrations of eteplirsen will be listed and summarized. 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.

4. STUDY OVERVIEW

4.1. 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 (eteplirsen-treated group), as compared with an untreated control arm of DMD patients amenable to exon skipping (untreated control group). Note that patients in the untreated control arm are not amenable to exon 51 skipping.

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 eteplirsen-treated group will receive once weekly intravenous 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.

An overview of the study design through Week 96 is presented in Figure 1.

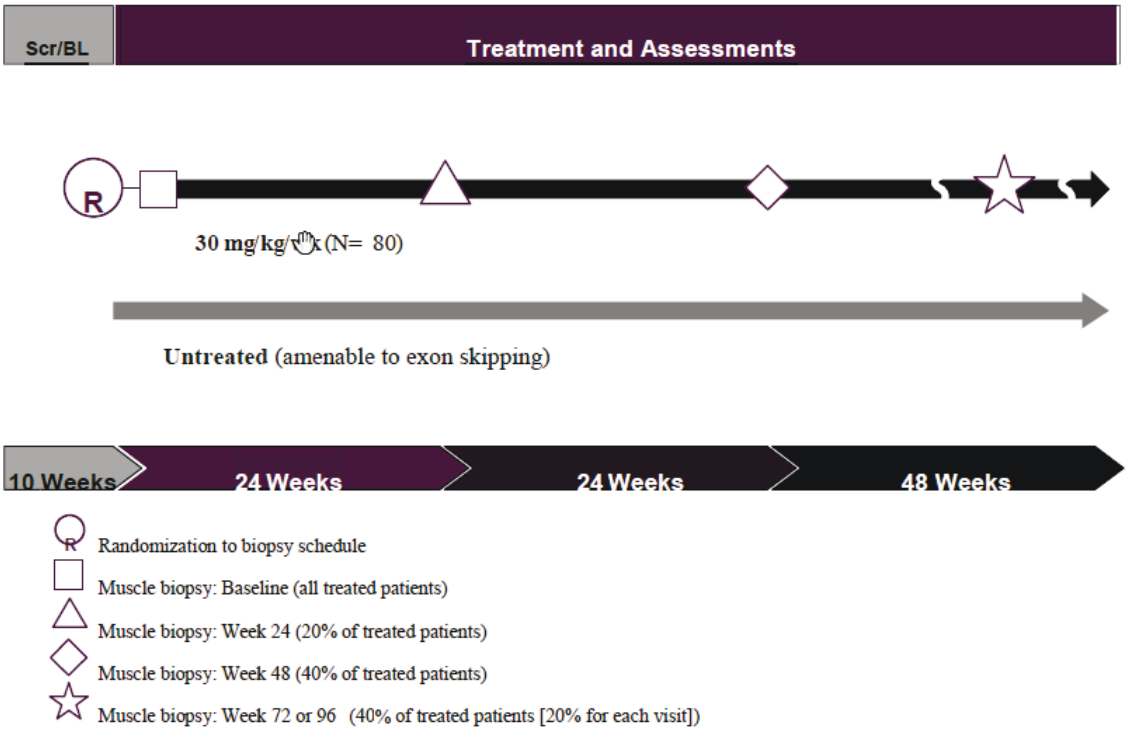

Figure 1 Overview of Study Design through Week 96

4.2. Sample Size and Power

This study will enroll approximately 90 patients with a 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

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

4.3. Randomization and Blinding

There will be no randomization for the assignment of patients to the 2 treatment groups (eteplirsen-treated vs untreated control). Patients who are amenable to exon 51 skipping will be assigned to the eteplirsen-treated group and receive weekly infusions of eteplirsen 30 mg/kg; and patients who are not amenable to exon 51 skipping will be assigned to the untreated control group.

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

4.4. Planned Analyses

4.4.1 Interim Analysis

An interim analysis was performed after approximately 35 patients with a Baseline 6MWT between 300 and 450 meters, inclusive, had completed their Week 96 study assessments.

This interim analysis was detailed in a separate SAP which was finalized on 28 Jun 2017.

4.4.2 Final Analysis

A final analysis of safety and efficacy will be conducted once the last patient completes the entire study and the resulting database is cleaned, quality assured, locked, and unblinded. 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. Due to the small population size and large dropout rate of the untreated control group, only descriptive summaries will be presented. An external control dataset will be identified and used to evaluate the effect of eteplirsen treatment. The statistical methods for the identification and use of the external control dataset will be presented in a supplemental SAP.

5. ANALYSIS SETS

The following analysis sets will be defined.

5.1. Efficacy Set

The efficacy set will consist of all patients in the eteplirsen-treated and untreated control groups who have at least 1 post-baseline functional assessment.

5.2. Primary Efficacy Set

The primary efficacy set will consist of all patients in the efficacy set who have a Baseline 6MWT distance of 300 to 450 meters, inclusive.

5.3. Safety Set

The Safety Set will consist of all patients who are enrolled in the study and either receive at least 1 dose of eteplirsen in the eteplirsen-treated group or have at least 1 post-Baseline safety assessment in the untreated control group.

For patients in the untreated control group, any safety assessment (including AE assessment) on or after the Week 1 visit, will be considered a post-Baseline safety assessment.

5.4. Muscle Biopsy Set

The muscle biopsy set will consist all patients who receive at least 1 dose of eteplirsen and have both baseline and 1 post-dose muscle biopsy sample evaluable for dystrophin expression.

5.5. Pharmacokinetic Set

The PK dataset will consist of all patients in the eteplirsen-treated group who receive a full dose of eteplirsen at the visits where PK sampling was done and for whom there are adequate PK samples from which to estimate population PK parameters.

6. GENERAL STATISTICAL METHODS AND CONVENTIONS

6.1. General Methods

Summary statistics will be presented by treatment group, unless stated otherwise.

For continuous variables, descriptive statistics will include the number of patients with data to be summarized (n), mean, SD, 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.

For time-to-event data with censoring, the Kaplan-Meier (KM) method will be used to summarize the data.

6.2. Handling of Missing Data

6.2.1 Imputation of Missing Values

6WMT distance
If the patient is confirmed to have LOA (section 6.7), a value of 0 (zero) meters will be imputed for any missing values at the time or after the confirmation of LOA.

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NSAA item and total score
If 4 or fewer of 17 NSAA items are missing, the score for the missing items will be assigned a value of zero. The NSAA total score will be calculated as the sum of the scores for the completed items. The total NSAA score will be treated as missing values when 5 or more items are missing.

6.2.2 Imputation of Missing Laboratory Values

Laboratory data that are continuous in nature, but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus 2 significant digits, respectively (eg, if the results of the continuous laboratory test is <20 or 2.0, a value of 19.99 or 1.99, respectively, will be assigned in computing summary statistics). Kidney injury molecule-1 (KIM-1) values that are reported as below the level of quantitation (<0.112) will deviate from the above rule and will be imputed as 0.099.

6.2.3 Handling of Incomplete Dates

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 follows:

- 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 or missing 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 and within 28 days of the last dose of eteplirsen for treated patients, or if the month and/or year of the onset date are on or after the date of the qualifying visit for untreated control patients.
- 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 only the year is known, December 31st of the recorded year will be used.

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

6.2.4 Imputation of Relationship or Severity for Adverse Events

In the summary of AEs, events with missing relationship or severity will be presented as “Related” or "Severe", respectively. However, missing values will be presented in the data listings as missing.

6.3. Multiple Testing and Comparisons

Because no comparisons between the eteplirsen-treated and untreated control groups will be performed, no adjustment will be made for multiple testing.

6.4. Adjustment for Covariates

Because no comparisons between the eteplirsen-treated and untreated control groups will be performed, adjustment for covariates is not applicable.

6.5. Subgroups

There are 2 subsets of patients based on their 6MWT distance at Baseline:

- 300-450 meters (Primary Efficacy Set)
- >450 meters

Analyses of the primary and secondary efficacy endpoints will be performed separately on each of the two subsets, as well as the total population.

The primary efficacy endpoint may be summarized for each of the following baseline subgroups:

- Baseline 6MWT distance (<370 vs ≥370 meters)
- Age (<9 vs ≥9 years old)
- Prior exposure to drisapersen (Yes vs No)

The following subgroups may be used in the summary of selected safety endpoints:

- Prior exposure to drisapersen (Yes vs No)

6.6. Presentations Over Time

For endpoints that are collected serially over time (eg, 6MWT distance, clinical laboratory tests), assessments/test values will be assigned to a specific time point (eg, 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 assessment may be used in the summary by time point if the unscheduled assessment was within 2 weeks of a missing scheduled assessment.

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

6.7. Definitions and Terminology

Day 1

Day 1 will be defined as the date of the first eteplirsen dosing for eteplirsen-treated patients, or the Week 1 visit date for untreated control patients.

Study Day

Study day will be defined as Event Date – Day 1 + 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.

Duration on Eteplirsen

Duration on eteplirsen will be calculated as the duration in weeks from Day 1 to the date of the last eteplirsen administration as recorded on the STUDY DRUG ADMINISTRATION eCRF plus 6 days (ie, [last dose – first dose date + 1 + 6]/7).

Duration in weeks calculated above will be then categorized to 1 of the following intervals: <24, 24 to <48, 48 to <72, 72 to < 96, or ≥96.

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 a 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 of 0.1 or above is rounded up (eg 25.14 mL is rounded up to 26 mL) and any volume below 0.1 is rounded down (eg 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.

Baseline Visit and Baseline value

Baseline visit will be considered the last visit prior to the initiation of eteplirsen for eteplirsen-treated patients, or the last visit on or before the Week 1 visit for untreated control patients. For any assessment that is taken on 2 consecutive days at baseline visit the base visit (ie, 6MWT, NSAA items and total score, FVC % predicted), the average value will be considered as the baseline value. If the assessment is taken or available only on 1 day at baseline visit, then the value on that day will be used as baseline value.

Change from Baseline

Change from Baseline will be calculated as follows:

Change from Baseline = Post-Baseline Value – Baseline Value

Percent Change from Baseline

Percent change from Baseline will be calculated as follows:

*Percent change from Baseline = (Change from Baseline / Baseline Value) *100*

Treatment-emergent Adverse Event

An AE will be considered treatment-emergent if it occurs 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 eteplirsen-treated patients, or on or after the Week 1 visit date for untreated control patients.

To define treatment emergence for AEs with missing onset or stop date or time, the following additional criteria will be used:

If both start and stop dates for a particular AE are missing, then the AE is considered treatment emergent.

- If onset date for a particular AE is missing, and stop dates falls after the first date/time, then that AE is considered treatment emergent.

- If onset date for a particular AE is the same as the first dose date and the start times missing, and stop dates falls after the first date/time, then that AE is considered treatment emergent.

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

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 eteplirsen-treated patients or occurring or worsening on or after the Week 1 visit for untreated control patients.

Prior Medication

A prior medication will be any medication taken and completed prior to the first dose of eteplirsen for eteplirsen-treated patients, or before the Week 1 visit for untreated control 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 dosing and ending 28 days after the last dose of eteplirsen for eteplirsen-treated patients, or on or after the Week 1 visit for untreated control patients.

Previous Drisapersen Exposure Status

A patient will be considered as having previous exposure to drisapersen if he had taken any drisapersen prior to Day 1 in this study (value=Yes); otherwise a patient will be considered as not having a previous exposure to drisapersen (value=No).

Time Since DMD Diagnosis

The time since DMD diagnosis, in months, will be calculated as (Day 1 – Date of DMD diagnosis + 1)/30.4375.

Duration of Corticosteroid Treatment

The duration of corticosteroid treatment, in months, will be calculated as (Day 1 – Date on which the patient started corticosteroid treatment + 1)/30.4375.

Corticosteroid Schedule

Corticosteroid schedules will include:

- Continuous (daily)
- Intermittent (includes all dosing schedules that do not require the patient to take at least one dose per day)

Non-Ambulatory Status and Loss of Ambulation (LOA)

The non-ambulatory status will be considered as “Yes” if all 3 conditions below are met:

- NSAA walk subscore as "0" (unable to achieve goal independently) on 2 consecutive days within a visit or NSAA was not done due to reason related to non-ambulation
- 6-minute walk test was not done with any reason related to permanent non-ambulation
- No later data showing this patient is still ambulatory. This is not required if non-ambulatory status occurs at the time of early withdrawal, or at the end of Week 96 assessment.

Note, when the NSAA or 6MWT is "Not Done" and the patient meets the non-ambulatory requirements above, a query will be issued to sites to confirm the permanence of non-ambulatory status. Prior to final database lock, the results of queries will be reviewed by Medical Director and Data Management and provided as documentation for non-ambulatory status determination.

Time to LOA is defined as the time from the initiation of eteplirsen for eteplirsen-treated patients, or Week 1 visit for untreated control patients to the first time of permanent non-ambulation. Patients who do not lose ambulation at the time of early withdrawal, or at the end of Week 96 assessment, whichever is earlier, the patient will be censored at the last time at which the patient is determined to be ambulatory.

NSAA and Total Score

The NSAA is a clinician-administered scale specifically designed for DMD patients that rates patient performance on various functional activities. Patients will be asked to perform 17 different functional activities including: stand, walk, stand up from chair, stand on one leg - right, stand on one leg - left, climb box step - right, climb box step - left, descend box step - right, descend box step - left, lift head, get to standing, rise from floor, stand on heels, jump, hop right leg, hop left leg, run 10 meters. Patients will be graded as follows

- 2 = achieves goal without any assistance;
- 1 = modified method but achieves goal independent of physical assistance from another person; and
- 0 = unable to achieve goal independently.

A total score is derived by summing the scores for all the individual items. The total score can range from 0 (if all the activities are failed) to 34 (if all the activities are achieved). All items should be tested without thoracic braces or leg orthoses. The scale is generally completed in a maximum of 15 minutes.

Ability to Rise Independently from the Floor

The ability to rise independently from the floor (without external support) is indicated by a NSAA subscore greater than 0 (unable to achieve goal independently). To considered as loss of ability to rise independently for any visit, the NSAA rise from floor subscore has to be zero on 2 consecutive days within a visit or NSAA missing due to reasons related to not able to accomplish the task.

The permanent loss of ability to rise independently from the floor to a patient is considered to have occurred at a specific visit if this visit as well as all subsequent visits, if any, all showed the loss of ability to rise independently from the floor.

For patients who were able to rise at baseline, time to the permanent loss of ability to rise independently from the floor is defined as the time from the initiation of eteplirsen for eteplirsen-treated patients, or Week 1 visit for untreated control patients to the first time of permanent loss of ability to rise independently; patients who do not experience permanent loss of ability to rise independently from the floor at the time of early withdrawal, or at the end of Week 96 assessment, whichever is earlier, the patient will be censored at the last time at which the patient is determined to be able to rise independently.

FVC% predicted, CCI [redacted]

FVC% predicted will be calculated using the prediction equations described by Hankinson (Hankinson et al, (1999 [1]) based on patient's age, and height as following:

FVC% predicted =100*FVC / (b0 + b1 * age + b2 * age^2 + b3 * height^2, where b0, b1, b2, and b3 are coefficients).

CCI [redacted]

Calculated Height

Calculated height will be used based on the following formula:

Height (cm) = 4.605U + 1.308A + 28.003

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

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[redacted]

6.8. 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.
- Study Day will appear in the data listings as appropriate.
- Date variables will be formatted as DDMMMYYYY for presentation. In the case of missing day, month, and/or year information, "UN", "UNK", or "UNKN" will be presented. For example, a date with a missing month and day will be presented as UNUNKYYYY.
- SAS® Version 9.4 or higher will be the statistical software package used for all analyses unless otherwise specified.
- R version 3.2.2 or higher and DAAG package 1.22 or higher will be used for the one-sample permutation test.
- The CDISC Study Data Tabulation Model Implementation Guide (SDTMIG) V3.2 for preparing data set will be used for this study.
- Tables, figures, and listings will be presented in landscape orientation.
- Listings will be sorted by treatment group, patient, and then date, unless otherwise specified.

7. STATISTICAL ANALYSES

7.1. Patient Disposition

Patient disposition will be summarized by treatment group for all patients enrolled and will include the frequency count and percentage for the following items: patients in the Safety Set, patients in the efficacy set, patients in the primary efficacy set, patients in the efficacy set with Baseline 6MWT > 450, patients who were randomized to a second biopsy (eteplirsen-treated patients only), patients who were treated, patients who completed the Week 96 efficacy visit, patients who completed the study, and patients who discontinued early. The reasons for discontinuation will also be summarized. Descriptive statistics will be presented for weeks on study.

An additional summary will be produced for the primary efficacy set.

Patient disposition and patient eligibility will be presented in data listings.

7.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the safety set. These variables will include age (years), race, ethnicity, Baseline height (cm), Baseline weight (kg), Baseline body mass index (kg/m^2), time since DMD diagnosis (months) at Baseline, mutation type(s), previous drisapersen exposure status, corticosteroid medication, corticosteroid schedule, duration of prior corticosteroid use at Baseline, prior physiotherapeutic interventions (within 3 months prior to the study: Yes vs No), and Baseline 6MWT distance.

An additional summary will be produced for the primary efficacy set and for the subset of patients with Baseline 6MWT > 450 meters.

Patient-level demographic data and baseline characteristics will be presented in data listings.

7.3. Prior and Concomitant Medications

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

All medications, whether prior or concomitant, will be presented in data listings. Separate listings of glucocorticoids and prior experimental DMD drugs will be presented.

7.4. Medical History

Medical history data for the Safety Set will be presented in data listings.

7.5. Physiotherapeutic Interventions

Physiotherapeutic interventions will be presented in data listings.

7.6. Protocol Deviations

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

7.7. Exposure to Study Drug

The exposure to eteplirsen will be summarized for eteplirsen-treated patients in the Safety Set. The variables will include the following (as applicable): cumulative exposure administered (mg), number of infusions of treatment, and duration on eteplirsen (weeks). Additionally, duration on eteplirsen category will be summarized for the following intervals: < 24 weeks, 24 to < 48 weeks, 48 to < 72 weeks, 72 to < 96 weeks, and ≥ 96 weeks.

Patient-level study drug information will be provided in a data listing. Additionally, a listing of the derived exposure parameters listed above will be generated as well as a listing of overdoses. The actual dose will be compared to the planned dose (Section 6.7). Any actual dose that is greater than 1.10 times the planned dose will be considered an overdose. Planned dose is calculated as the dose level in mg/kg multiplied by the patient's most recent weight prior to the dose (or on the same day with no time).

7.8. Efficacy Analyses

For any efficacy assessment that is taken on 2 consecutive days within a visit (ie, 6MWT, NSAA items and total score, FVC % predicted), the average value will be used. If the assessment is taken or available only on 1 day, then the value on that day will be used. A value that is marked as invalid or not completed successfully on the eCRF will be considered a missing value.

Analyses of the primary and secondary efficacy endpoints will be performed separately on the primary efficacy set, the efficacy set, and the subset of patients with Baseline 6MWT distance >450 meters.

Due to the high dropout rate in the untreated group, comparisons between the eteplirsen-treated group and the untreated control group will not be meaningful. Therefore, only summaries by treatment group will be presented.

7.8.1 Analyses of Primary Efficacy Endpoint

Missing 6MWT values will be imputed as specified in Section 6.2.1.

The primary efficacy endpoint, change from baseline at Week 96 in 6MWT distance, will be summarized as part of the by-visit summary for 6MWT.

Observed 6MWT distance and change from baseline will be summarized by treatment group and visit using descriptive statistics. A plot of the mean (+/- SE) of change from baseline in 6MWT distance will be generated.

In addition, summaries by Baseline 6MWT and Baseline age subgroups (see Section 6.5) may be presented for the primary efficacy set.

7.8.2 Analyses of Secondary Efficacy Endpoints

Ability to Rise Independently from the Floor

The number and percentage of patients who are able to rise from the floor independently will be summarized by treatment group for each visit.

Time to Loss of to Rise Independently from the Floor

Time to permanent loss of ability to rise independently will be summarized. The number of patients who lost the ability, and the number of patients censored will be presented by treatment group. The percentages of patients remaining able to rise from the floor independently at 12, 24, 36, 48, 72, and 96 weeks, as estimated using the KM method, will be presented by treatment group.

The time to permanent loss of the ability to rise independently will be plotted by treatment group using the KM method, with the percentage of patients remaining able to rise being the vertical axis and time on study in weeks being the x-axis. The plot will include the number of patients at risk for each treatment group over time. The median times to loss of the ability to rise and associated 95% confidence intervals will be estimated using KM method.

Loss of Ambulation (LOA)

Time to LOA will be summarized by treatment group. The number of patients who lost ambulation, and the number of patients censored will be presented by treatment group. The percentages of patients remaining ambulatory at 12, 24, 36, 48, 72, and 96 weeks, as estimated using the KM method, will be presented by treatment group.

The time to LOA will also be plotted by each treatment group using the KM method, with the percentage of patients remaining ambulatory being the vertical axis and time on study in weeks being the x-axis. The plot will include the number of patients at risk for each treatment group over time. The median times to LOA and associated 95% confidence intervals will be estimated using KM method.

A data listing of time to LOA will be presented, which will include the censoring information.

Change from Baseline in FVC Percent Predicted

FVC% predicted is one of the three most important parameters gained from the pulmonary function tests. Observed FVC % predicted and change from Baseline will be summarized by treatment group and visit using descriptive statistics. A plot of the mean (+/- SE) of change from baseline in FVC % predicted will be generated.

Change from Baseline in NSAA Total Score

Observed NSAA total score and change from Baseline will be summarized by treatment group and visit using descriptive statistics. A plot of the mean (+/- SE) of change from baseline in NSAA total score will be generated.

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7.8.4 Muscle Biopsy Endpoints

Quantity of Dystrophin Protein Expression as Measured by Western Blot

For each time point, 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 below the lower limit of detection or the lower limit of quantification, different imputation methods will be used (Table 1). The limit of detection (LOD) is 0.05 (% normal), lower limit of quantification (LLOQ) is 0.25 (% normal). Values less than LLOQ will be imputed using 1 of 4 methods: as lower bound (0 or 0.05), as upper bound (0.04 or 0.24, middle value (0.02 or 0.15) 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. Samples with values above the upper limit of quantitation (8.0% normal) will not be imputed. Samples will be diluted in order to generate a number

within the measuring range. The as-measured value, adjusted for dilution factor, will be reported.

Table 1: Imputation Method for Values Outside of the Limits for Western blot

Imputation type	Treat value < LLOQ as	Analysis type
1	As measured	Main analysis
2	Using lower bound for imputation 0 ~ <LOD as 0 LOD ~ <LLOQ as 0.05	Sensitivity analysis
3	Using upper bound for imputation 0 ~ <LOD as 0.04 LOD ~ <LLOQ as 0.24	Sensitivity analysis
4	Using middle value for imputation 0 ~ <LOD as 0.02 LOD ~ <LLOQ as 0.15	Sensitivity analysis

LOD=limit of detection; LLOQ=lower limit of quantification

Dystrophin level (% normal) determined by Western blot will be summarized by visit. In addition, change from baseline and the fold change over baseline by visit will be summarized. Statistical summaries of observed values and change from baseline by visit will be presented in plots. A one-sample permutation test will be used to test the null hypothesis that the mean change from baseline in dystrophin level is 0 at each visit. Additionally, the by-visit analyses will be repeated pooling all post-baseline results together. A waterfall plot will be used to present each individual patient's data on the Western blot. Vertical bars are drawn for each patient, either above or below the baseline. The vertical (y) axis is the change from baseline by visit in dystrophin protein level determined by Western blot. The x-axis is the rank of the change from baseline. The waterfall plot is ordered from the worst value (lowest) on the left side to the best value (highest) on the right side. Additionally, box plots of change from Baseline will be presented by Baseline 6MWT Group (< 370 meters ≥370 to ≤ 450 meters, > 450 meters), Baseline Age Group (< 9 years, ≥ 9 year), previous drisapersen exposure (Yes, No) and genetic mutation type(exon 45-50, 48-50, 49-50, 50, other)

- Dystrophin level (% normal) for each gel and the average value at baseline and post-baseline: values at the gel level outside of the limits of quantification will be flagged.
- Change from baseline at post-baseline visit
- Fold change from baseline at post-baseline visit

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7.9. Safety Analyses

Analyses of safety data will include AEs, SAEs, AESIs, laboratory data, ECG and ECHO measurements, vital signs, and physical examinations.

Analysis of safety data will be based on the Safety Set.

Safety analyses will be descriptive in nature. All summaries will be by treatment group for the Safety Set.

Selected safety summaries and/or listings will be presented for the subset of patients with prior exposure to drisapersen. These will include:

- Overall Summary of Adverse Events

- Summary of Treatment-Emergent Adverse Events by SOC and PT

7.9.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 17.1 or higher). This coding system provides five levels to classify AEs. In general, AEs will be presented by system organ class (SOC) and PT but other classifications may be used if warranted.

The sorting order for the AE incidence tables, unless otherwise specified, will be by decreasing frequency in the active treatment arm. Multiple occurrences of the same AE (at the PT level) in the same patient will be counted only once in the frequency tables. If a patient experiences multiple episodes of the same event with different 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. For example, for the table of AEs by SOC and PTs sorted by decreasing frequency presented by treatment group, SOC will be presented in decreasing frequency order of the active treatment column, and within each SOC, PTs will be presented in decreasing order of active treatment column. A patient is counted only once within each SOC and PT.

If a patient experiences multiple events that map to a single PT, the maximal severity grade and strongest investigator assessment of relation to study medication will be assigned to the PT for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having a severity of "SEVERE" and/or a "DEFINITELY RELATED" relationship to study medication.

An overall summary of AEs table will be presented which will include:

- Number of Treatment-emergent AEs (TEAEs)
- Number of TEAEs by Severity
- Number of patients with at least 1 TEAE
- Number of patients with at least 1 Severe TEAE
- Number of patients with at least 1 treatment-related TEAE
- Number of patients with at least 1 treatment-emergent SAE
- Number of patients with at least 1 treatment-related, treatment-emergent SAE
- Number of patients with at least 1 TEAE leading to discontinuation of study drug
- Number of patients with a TEAE leading to death

Treatment-Emergent AEs (TEAEs)

The following TEAEs summary tables will be presented by treatment group:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity

- TEAEs by descending frequency of PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT, and severity
- Treatment-related TEAEs by descending frequency of PT
- TEAEs reported in ≥10% of patients in any treatment group (upon examination of the actual data, different cut-off points may be used to examine the incidence of these AEs if it is deemed appropriate)
- TEAEs reported in ≥2% of patients in the active treatment group (and greater than untreated group)

The following listings will be produced:

- Listing of non-TEAEs
- Listing of TEAEs
- Listing of TEAEs leading to discontinuation of study drug
- Listing of TEAEs leading to withdrawal from study

Listings will include all data with an indicator for treatment period for each record when the event occurred.

Serious Adverse Events and Deaths

The following summary tables will be produced:

- treatment-emergent nonserious AEs
- treatment-emergent SAEs
- treatment-related, treatment-emergent SAEs
- deaths and AEs resulting in death
- AEs leading to study drug discontinuation by SOC and PT

The following listings will be produced:

- Listing of all AEs
- Listing of AEs leading to discontinuation
- Listing of SAEs (including pre-dosing SAEs)
- Listing of death
- Listing of SAEs that occurred prior to the initiation of study drug or after 28 days post-last dose will be excluded from the tables but will be included in the listing at the start date/time of the AE.
- Listing of AEs related to study procedure by SOC and PT

Listings will include all data with an indicator for treatment period for each record when the event occurred.

A summary of deaths and reasons for deaths will be presented by Analysis period and treatment group. A patient-level listing will be provided.

Adverse Events of Special Interest

Summaries of AEs of special interest will be summarized by SOC and PT. All standardised MedDRA Queries ([SMQs]) listed below will include broad and narrow terms. The 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 occurring on the same date as an infusion where infusion start time or AE onset time was not reported])

Prior to statistical analysis, for all IRRs as defined above, IRRs will be medically reviewed 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 medically reviewed IRRs. In addition, all IRRs as defined above that meet the following criteria will be excluded from the list of medically reviewed 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

Summaries of all medically reviewed IRRs and medically reviewed IRRs with event start time reported be generated separately. In addition, a summary table will be generated and include the following:

- Number of patients with medically reviewed IRRs
- Number of medically reviewed IRRs
- Number of medically reviewed IRRs with event start time reported
- Number of events on any day for medically reviewed 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 and/or moderate or severe will be produced. An overall summary of AESI events will include total number of events, number of SAEs, number of treatment-related events, number of unrelated 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 (within 24 hours or on the same day

with no time). A listing of each AESI category and a listing of AEs related to study drug for each AESI strategy will be generated.

Additional AEs for Review

Additional AEs for review will be summarized by SOC and PT All SMQs listed below will include broad and narrow terms. The AEs for additional 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)
- Coagulopathy (Hemorrhage terms [excluding lab terms] SMQ, Hematopoietic thrombocytopenia SMQ, and PTs in the Embolism and thrombosis High Level Group Terms)
- Leukopenia/Neutropenia/Haematologic toxicity (Hematopoietic leukopenia SMQ)

An overall summary of additional AE for review will include total number of events, number of SAEs, number of treatment-related events, number of unrelated 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.

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 and/or moderate or severe will be produced.

7.9.2 Clinical Laboratory Evaluations

Analyses of clinical laboratory values will be performed. Normal ranges will be determined based on the ranges supplied by the central laboratory (with appropriate conversion to standard units). Baseline, the highest/lowest value postbaseline, and the final observation will be presented for each laboratory assessment for each treatment group.

Descriptive statistics will be calculated for the observed values as well as the change from baseline values. The highest value will be summarized for alanine aminotransferase (ALT), alkaline phosphatase, amylase, aspartate aminotransferase (AST), C-reactive protein, creatine kinase, creatinine, cystatin C, gamma glutamyltransferase, lactate dehydrogenase, total bilirubin, uric acid, absolute basophils, absolute eosinophils, basophil percent, eosinophil percent, activated partial thromboplastin time, international normalized ratio, prothrombin time, urine KIM-1, and urine protein. The lowest observation will be summarized for albumin, and platelets.

Both the highest value and the lowest value will be summarized for blood urea nitrogen, calcium, chloride, glucose, potassium, protein, sodium, absolute lymphocytes, absolute monocytes, absolute neutrophils, hematocrit, hemoglobin, lymphocyte percent, monocyte percent, neutrophils percent, white blood cell count, urine pH, and specific gravity. Shifts from baseline to the highest/lowest postbaseline value and final observation will be summarized for each treatment group. Additionally, the highest/lowest and final observation in the treatment period will be presented for summary of laboratory shifts. Frequencies in a shift table will be calculated within each treatment and baseline classification.

A table of frequencies of potentially clinically significant laboratory abnormalities, or abnormalities of interest that occur after baseline as defined in Appendix Table 1, Appendix Table 2, and Appendix Table 3 will be generated by treatment. Additionally, a table of patients who met Hy's law will be generated by treatment. Hy's law will be defined as:

(ALT or AST > 2 x Baseline) and/or (Total Bilirubin > 2 x Upper Limit of Normal [ULN])

All laboratory values with any abnormalities of interest will be listed. Additionally, laboratory values that are outside of the normal range will be listed separately.

7.9.3 Vital Signs and Other Physical Findings

Vital signs will be summarized by treatment group using descriptive statistics. For each vital sign, the baseline and final observations will be presented by treatment group. Additionally, the largest absolute change from baseline for systolic blood pressure and diastolic blood pressure, the highest value of pulse rate, and the largest absolute change in respiration rate will be summarized. Descriptive statistics will be calculated for the observed values as well as the change from baseline values.

A table of frequencies of vital sign abnormalities of interest that occur after baseline as defined in Appendix Table 4 will be generated by treatment. The number and percentage of patients experiencing the abnormality as well as the total number of abnormalities will be presented. All vital sign values with an abnormality of interest will be listed. Abnormal physical examination results will be listed.

7.9.4 Electrocardiograms and Echocardiograms

Electrocardiogram (ECG) and echocardiogram (ECHO) assessments will be summarized by treatment group using descriptive statistics. For each ECG and ECHO parameter, the baseline and final observations will be presented by treatment group. Additionally, the largest change from baseline QT interval corrected for heart rate, QRS, and PR intervals, the highest value of QT and the largest absolute change for heart rate will be summarized. Descriptive statistics will be calculated for the observed values as well as the change from baseline values.

A table of frequencies of ECG and ECHO abnormalities of interest that occur after baseline as defined in Appendix Table 5 will be generated by treatment. The number and

percentage of patients experiencing the abnormality as well as the total number of abnormalities will be presented. All ECGs and ECHOs with an abnormality will be listed.

7.10. 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.

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

8. CHANGES IN PLANNED ANALYSES

8.1. Changes from Protocol-Planned Analyses

The following changes were made compared to the protocol-planned analyses:

- Comparisons between the eteplirsen-treated group and the untreated control group will not be performed due to the expected very small number of patients in the untreated control group and the differences in the populations between the treated and untreated groups. No hypothesis test, no p-value and no inferential statistics will be made for comparison of eteplirsen treated patients and untreated patients
- 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.
- Renamed "predefined change abnormal" to "predefined markedly abnormal" for clinical laboratory tests and other safety endpoints.
- CCI [redacted]

8.2. Changes from Previous Statistical Analysis Plans

The following changes were made compared to the previous SAP (SAP 1.1):

- Updated imputations for Western Blot sensitivity analyses

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- Added box plot figures for each dystrophin-expression endpoint

9. REFERENCES

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2. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax. 1984;39(7):535-8.
3. Domenech-Clar R, Lopez-Andreu JA, Compte-Torrero L, De Diego-Damia A, Macian-Gisbert V, Perpina-Tordera M, et al. Maximal static respiratory pressures in children and adolescents. Pediatr Pulmonol. 2003;35(2):126-32.

10. APPENDIX:

10.1. Criteria of Abnormalities

Appendix Table 1 Chemistry Laboratory Abnormalities of Interest

Test	Unit	Predefined Change From Baseline		Markedly Abnormal Criteria
		Decrease	Increase	
Blood urea nitrogen	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[b]	mmol/L	0.30	0.30	NA
AST	U/L	NA	NA	Value ≥ 2× Baseline Value
ALT	U/L	NA	NA	Value ≥ 2× Baseline Value
Gamma glutamyl transferase	U/L	NA	NA	Value > 3X Baseline OR > ULN
Alkaline phosphatase	U/L	NA	NA	Value > 1.5 × ULN
Albumin	g/dL	1	1	< LLN or > ULN
Total bilirubin[d]	μmol/L	NA	10	Value > 1.5× ULN
Lactate dehydrogenase	U/L	NA	NA	Value ≥ 2× Baseline Value
Creatine kinase	U/L	NA	NA	Value ≥ 2× Baseline Value
Cystatin C	mg/L	NA	NA	> ULN

[a]Convert to SI unit by multiplying mg/dL value by 0.0555
[b]multiply mg/dL value by 0.25;
[c]multiply g/dL value by 10
[d]multiply mg/dL value by 17.1.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; 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 from Baseline 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+
Hemoglobin/blood in urine	Positive (+)
RBC 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/minute	< 12	> 20
Temperature	°C	< 36.0	> 38.0
Weight	kg	Decrease of 7% or more from Baseline	

Appendix Table 5 Electrocardiogram and Echocardiogram Abnormalities of Interest

Variable	Units	LLN	ULN	Age Group (years)	Markedly Abnormal Criteria
Heart Rate	beats / minute	60	130	NA	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
LVEF	%	NA	NA	All	< 55%
Fractional shortening	%	NA	NA	All	< 29%

IVCD = intraventricular conduction delay; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; QTcF = QT interval corrected by Fridericia's correction; ULN = upper limit of normal

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