STATISTICAL ANALYSIS PLAN

Protocol 4658-102 [redacted]

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

[redacted]

4658-102: Version 4, 07 February 2020

[redacted]

Date: 14 April 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Expanded Term
ADaM IG	Analysis Data Model Implementation Guide
AE	Adverse Event
AESI	Adverse Event of Special Interest
Ae%	Amount of drug eliminated in urine
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-curve
CL	Total clearance
C_{max}	Maximum plasma concentration
[redacted]	[redacted]
CDISC	Clinical Data Interchange Standards Consortium
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DMD	Duchenne Muscular Dystrophy
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram/Echocardiography
GCP	Good Clinical Practices
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
IVAD	Implantable Venous Access Device
KIM-1	Kidney Injury Moledule-1
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]

PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM IG	Study Data Tabulation Model Implementation Guide
SMQ	Standard MedDRA Query
SOC	System Organ Class
t½	Elimination half-life
TEAE	Treatment Emergent Adverse Event
Tmax	Time to maximum plasma concentration
V_{ss}	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 4658-102, entitled "An Open-Label Safety, Tolerability, and Pharmacokinetics Study of Eteplirsen in Young Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping" [redacted]

This SAP has been prepared based on Protocol Version 4, dated 07 February 2020 for Study 4658-102, [redacted]

2. STUDY OBJECTIVES

Study 4658-102

Primary Objective:

The primary objective of Study 4658-102 is to evaluate the safety and tolerability of eteplirsen administered once weekly by intravenous (IV) infusion in male Duchenne muscular dystrophy (DMD) patients ages 6 months to 48 months, inclusive.

Secondary Objective:

The secondary objective of Study 4658-102 is to determine the pharmacokinetics (PK) of eteplirsen at the 2, 10, 20, and 30-mg/kg dose levels administered once weekly by IV infusion in male DMD patients ages 6 months to 48 months, inclusive.

[redacted]

3. STUDY ENDPOINTS AND OTHER VARIABLES

The study endpoints for which the statistical methods will be described in this SAP comprise of safety, PK, and efficacy endpoints.

Study 4658-102

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

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

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

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

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

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

[redacted]

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

4. STUDY DESCRIPTION

4.1. Study Overview

Study 4658-102

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

Patients will be evaluated for inclusion during the Screening Period of up to 2 weeks to assess eligibility. Written informed consent from the parent/legal guardian to participate in the study must be obtained prior to beginning any study-related procedures.

Patients will be enrolled into 1 of 2 age cohorts: Cohort 1 of approximately 6 male patients age 24 to 48 months and Cohort 2 of approximately 6 male patients age 6 months to <24 months.

After the first 3 patients in Cohort 1 have completed 12 weeks of eteplirsen therapy, including 2 infusions each at 2, 4, 10 and 20 mg/kg and 4 infusions at 30 mg/kg, the Data Monitoring Committee (DMC) will review the safety data and determine whether to begin enrollment of the younger patients (Cohort 2). The DMC will also review safety data at least weekly through the first 12 weeks of dosing for the first 3 patients of each age cohort. Reviews will be at least quarterly thereafter.

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

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

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

[redacted]

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

[redacted]

4.2. [redacted]

[redacted]

4.3. Randomization and Blinding

Both 4658-102 [redacted] are open-label single arm studies and, therefore, all patients will receive eteplirsen.

4.4. Planned Analyses

4.4.1 Safety Review

The DMC will be comprised of a group of individuals with pertinent methodological and clinical expertise relevant to the study design and background population, to review the conduct of the study and the emerging safety, PK, and efficacy data on an ongoing basis

in order to ensure that clinical trial participants are not exposed to unreasonable or unnecessary risks. The DMC will advise the study team and study investigators on safety aspects of dose interruption/continuation and dose escalation for the study. The DMC will begin their duty before the start of the clinical trial and will continue for the entire duration of the study.

The activities and composition of this committee are outlined in the DMC Charter which was ratified during the initial DMC meeting, prior to the commencement of dosing of the study patients, on 24 June 2019. The reviews will be performed at least weekly through the first 12 weeks of dosing for the first 3 patients of each age cohort and at least quarterly thereafter. Oversight and monitoring of the clinical study by the DMC will be performed in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. These safety monitoring functions are distinct from the requirements for study review and approval by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

4.4.2 Final Analysis

Study 4658-102 final analysis of safety and efficacy will be conducted once the last patient completes the efficacy visit and the resulting database including AEs and concomitant medications is cleaned, quality assured, and locked through the data cut. [redacted] 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.

4.5. Analysis Set

[redacted]

The Safety set includes all patients who are enrolled in Study 4658-102 and receive at least 1 dose of eteplirsen while in Study 4658-102. This analysis set will be used for analyses of all endpoints for the 4658-102 Final Analysis, unless stated otherwise.

[redacted]

5. GENERAL STATISTICAL METHODS AND CONVENTIONS

5.1. General Methods

Summary statistics will be presented by cohort, unless stated otherwise.

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

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

Summaries will be for the following cohorts:

- Cohort 1 (age 24 to 48 months)
- Cohort 2 (age 6 to <24 months)

[redacted] All analyses will be displayed on the safety set for the final analysis of 4658-102. [redacted]

5.2. Handling of Missing Data

5.2.1 [redacted]

[redacted]

5.2.2 [redacted]

5.2.3 [redacted]

5.2.4 [redacted]

5.2.5 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 (e.g., if the results of the continuous laboratory test is <20 or <2.0, a value of 19.99 or 1.999, respectively, will be assigned in computing summary statistics; if the results of the continuous laboratory test is >20 or >2.0, a value of 20.01 or 2.001, 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.

5.2.6 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 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 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. If a partial AE onset

date is after the treatment end date, then the date will be imputed as the first day of the month.

- 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.

5.2.7 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.

5.3. Multiple Testing and Comparisons

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

5.4. Adjustment for Covariates

Not applicable.

5.5. Subgroups

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

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

5.7. Algorithm, Computation and Definition of Derived Variables

Day 1

Day 1 in Study 4658-102 will be defined as the date of the first eteplirsen administration in Study 4658-102.

[redacted]

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. Study Day will be defined for Study 4658-102 [redacted].

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 plus 7 days. This calculation will be performed for each study.

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 (i.e., [last dose – first dose date + 7]/7).

Duration in weeks calculated above will be then categorized to 1 of the following intervals for Study 4658-102: <24, 24 to <48, 48 to <72, 72 to < 96, and 96 weeks.

[redacted]

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 (e.g. 25.14 mL is rounded up to 26 mL) and any volume 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.

Patient Years on Eteplirsen

The patient years on eteplirsen will be calculated as (Last Treatment Date - First Treatment Date + 7)/365.25.

Baseline Visit

Baseline visit in Study 4658-102 will be considered the last visit prior to the initiation of eteplirsen in Study 4658-102.

[redacted]

Change from Baseline

Change from Baseline will be calculated as follows:

Change from Baseline = Post-Baseline Value – Baseline Value

The change may be classified into a categorical variable, as appropriate.

Percent Change from Baseline

Percent change from Baseline will be calculated as follows:

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

Percent change from Baseline will not be calculated if Baseline value is 0.

[redacted]

[redacted]

Treatment-emergent Adverse Event (TEAE)

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.

Treatment-related Adverse Event

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

Treatment-Emergent Laboratory, Vital Signs, ECGs, and ECHO Abnormality

A treatment-emergent laboratory, vital signs, ECGs, and ECHO abnormality will be defined as any laboratory, vital signs, ECGs, and ECHO abnormality occurring or worsening after the initiation of eteplirsen dosing and within 28 days of the last dose of eteplirsen.

Prior Medication

A prior medication will be any medication taken and completed prior to the first dose of eteplirsen.

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 within 28 days after the last dose of eteplirsen.

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) or other (including intermittent dosing such as Saturday and Sunday dosing only).

EudraCT Category

- In utero: Unborn infants, still in the womb.
- Preterm newborn: Subjects born before 37 weeks from their conception.
- Newborns: Newborn aged from birth to less than 28 days.
- Infants and toddlers: Subjects aged 28 days to less than 2 years.
- Children: Subjects aged 2 to 11 years.
- Adolescents: Subjects aged 12 to less than 18 years.

- Adults: Subjects aged 18 to 64 years.
- Adults: Subjects aged 65 to 84 years.
- Adults: Subjects aged 85 years and over.

5.8. 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 or provided file by vendor. 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.Y%), where the percentage is YY.Y.
- Percentages of patients with treatment-emergent abnormalities will be based on non-missing 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 V1.1 for preparing data sets will be used for this study.
- The CDISC Study Tabulation Model Implementation Guide 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 cohort, patient and then date unless otherwise specified.

6. STATISTICAL ANALYSES

6.1. Patient Disposition

For Study 4658-102, the number of patients enrolled, the number in Safety Set, the number and percentage of patients completing the study through Week 96, the number and percentage of patients prematurely discontinuing before Week 96, and the duration of study (weeks) will be summarized. Reasons for premature discontinuation will also be summarized. All analyses will be performed overall and by age cohort.

[redacted]

Patient eligibility and disposition will be presented in a listing.

6.2. Demographics and Baseline Characteristics

Demographic and Baseline characteristics will be summarized overall and by age cohort. These variables will include age (months), EudraCT age category, race, ethnicity, height/length (cm), weight (kg), BMI (kg/m^2), mutation, time from DMD diagnosis (months) to Baseline, corticosteroid medication type, corticosteroid frequency, duration of prior corticosteroid use at Baseline.

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

6.3. Prior and Concomitant Medications

Concomitant medications will be coded by preferred term using the most recent World Health Organization (WHO) Drug Dictionary (WHODRUG, December 2013). 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 preferred term by cohort. At each level of summarization, a patient is counted once if he/she reported one or more medications at that level. The summarization of concomitant medications for the Study 4658-102 final analysis will include all concomitant medications collected at the time of the Study 4658-102 data lock. [redacted]

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

6.4. Medical History

Medical history data for the safety set will be presented in data listings. The summarization will only be included for the Study 4658-102 final analysis [redacted]

6.5. Physiotherapeutic Interventions

A listing of all physiotherapeutic interventions will be provided.

6.6. 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). Additionally, major deviations will be summarized by deviation type. The listing and table will be summarized separately by whether the protocol deviations are related to COVID-19 or not.

6.7. Exposure to Study Drug

The exposure to eteplirsen will be summarized for eteplirsen-treated patients in the Safety Analysis Set. The variables will include the following (as applicable): total number of infusions received, total number of infusions on 30 mg/kg of eteplirsen received, cumulative amount of drug received (mg), duration on eteplirsen in 24-week intervals, and patient years on eteplirsen. For both the 4658-102 [redacted] final analyses, these endpoints will be calculated cumulatively [redacted]

Patient-level study drug information will be provided in a data listing. Additionally, a listing of the derived exposure parameters above will be generated as well as a listing of overdoses. The actual dose will be compared to the planned dose. Any actual dose that is greater than 1.10 times of 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).

6.8. Safety Analyses

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

6.8.1 Adverse Events

The final analysis of 4658-102 AE will include all data collected in 4658-102. [redacted]

In general, only TEAEs will be summarized. Nontreatment-emergent 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 System Organ Class (SOC) and Preferred Term (PT) and summarized overall and by age cohort.

An overall summary table of adverse events will be produced and will include:

- The frequency count and percentage of patients with:
  - A TEAE
  - A Treatment-related TEAE
  - A Severe TEAE
  - A Treatment-Emergent SAE
  - A Treatment-Emergent Related SAE
  - A TEAE leading to discontinuation of study drug
  - A TEAE leading to death
  - A Non-Serious TEAE
- The number of events
  - at each severity level (mild, moderate, severe)
  - that are non-serious
  - that are serious

Multiple occurrences of the same AE (at the preferred term level) in the same patient will be counted only once in frequency tables. If a patient experiences multiple episodes of the same event with different 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
- 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 related to study procedures by SOC and PT
- TEAEs related to underlying disease by SOC and PT
- Treatment-Emergent SAEs by SOC and PT
- Treatment-related Treatment-Emergent SAEs by SOC and PT
- Non-Serious TEAEs by SOC and PT

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

The following listings will be produced:

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

Additionally, summary tables of AEs by each one-year duration of eteplirsen (i.e., AEs at the 1st year of eterplirsen treatment, 2nd year, 3rd year, …, 6th year) will be provided.

6.8.2 Adverse Events of Special Interests

Summaries of TEAEs of special interest by SOC and PT will be summarized overall and by age cohort. 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:

- Nephrotoxicity
    - Proteinuria > 500 mg/24 hr
    - eGFR <60 ml/min/1.73 m^2
- Hepatotoxicity
    - GGT or GLDH > 8 × ULN
    - GGT or GLDH > 5 × ULN for more than 2 weeks
    - GGT or GLDH > 3 × ULN and (total bilirubin >2 × ULN or international normalized ratio > 1.5)
    - GGT or GLDH > 3 × ULN with the appearance of the following signs or symptoms: fatigue, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- Hypersensitivity
    - Anaphylaxis, anaphylactoid reaction, or angioedema
        - for Anaphylaxis use PT anaphylactic reaction, anaphylactic shock
        - for Anaphylactoid reaction use PT anaphylactoid reaction, anaphylactoid shock
        - for Angioedema use PTs angioedema, epiglottic oedema, laryngeal oedema, laryngotracheal oedema, lip oedema, swollen tongue, tongue oedema, tracheal oedema
    - Any severe allergic reaction (Hypersensitivity SMQ Broad & Narrow)
    - Any severe (Grade ≥3) infusion related reactions (IRRs) that occurred within 24 hrs.

- Any severe complement mediated, inflammation event (eg, acute kidney injury, arteritis, myocarditis, pneumonitis)

- Thrombocytopenia
  - Platelet count < 75,000/mm^3
- Infusion-related reactions
  - All adverse events with reported start time within 24 hours of the eteplirsen infusion if AE start clock time and infusion clock time is available OR occurred by the next calendar date if either AE start clock time or infusion clock time is not available.

An overall summary of adverse events of special interest 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 of AE of special interest. If applicable, a table corresponding to the adverse events of special interest that were related to study drug and/or moderate or severe will be produced.

6.8.3 Important Risks

Summaries of TEAEs possibly indicative of important risks by SOC and PT will be summarized overall and by age cohort. All standard MedDRA queries (SMQs based on MedDRA version 17.1) listed below will include broad and narrow terms unless noted.

- Nephrotoxicity:
  - Acute renal failure SMQ
  - HLT Glomerulonephritis and nephrotic syndrome
  - HLT Nephritis NEC
  - HLT Nephropathies and tubular disorder NEC
  - PT Hematuria (10018867)
- Hypersensitivity
  - Hypersensitivity SMQ
  - HLT Immune response protein analyses NEC
- Infusion related reaction: events occurring within 24 hours of infusion or the next calendar day if the time (AE onset or start of infusion) is missing. Medical adjudication will be performed to determine whether the event is a possible infusion related reaction.
- Hypersensitivity excluding medically reviewed infusion related reaction: Hypersensitivity SMQ events minus events adjudicated as possible IRRs.

An overall summary of adverse events of important risks 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 of AE of important risks. If applicable, a table corresponding to the adverse events of important risks that were related to study drug and/or moderate or severe will be produced.

6.8.4 Risks Associated with Other Antisense Oligonucleotides

All standard MedDRA queries (SMQs based on MedDRA version 17.1) listed below will include broad and narrow terms unless noted.

- Hepatotoxicity:
    - Hepatic failure SMQ
    - Fibrosis and cirrhosis and other liver damage-related conditions SMQ
    - Hepatitis, non-infectious SMQ
    - Cholestasis and jaundice of hepatic origin SMQ
    - Liver related investigations, signs and symptoms SMQ
    - Liver-related coagulation and bleeding disturbances SMQ
- Thrombocytopenia: Hematopoietic thrombocytopenia SMQ

An overall summary of adverse events of risks associated with other antisense oligonucleotides 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 of AE of risks associated with other antisense oligonucleotides.

6.8.5 Risks Associated with the Studied Population

All standard MedDRA queries (SMQs based on MedDRA version 17.1) listed below will include broad and narrow terms unless noted.

- Serious blood stream infections with implantable venous access device (IVAD):
    - Sepsis SMQ (available in MedDRA V22.1)
    - Toxic septic shock conditions SMQ Narrow
    - PT Vascular device infection
    - PT Bacteraemia, Viremia, Fungemia, Sepsis, or Septic shock
    - HLT Implant and catheter site reactions
    - HLGT Device issues

- Verbatim terms containing “port”, “central venous”, and “central line”

- Rhabdomyolysis: Rhabdomyolysis/myopathy SMQ

An overall summary of adverse events of risks associated with the studied population 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.

6.8.6 A corresponding listing will be generated for each of AE of risks associated with the studied population. Clinical Laboratory Evaluation

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 post-Baseline, and the final observation (within 28 days of the last dose of eteplirsen) 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 post-Baseline value and final observation will be summarized for age cohort and overall. 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 treatment-emergent markedly abnormal results that occur after Baseline as defined in Appendix Table 1, Appendix Table 2, and Appendix Table 3 will be generated overall and by age cohort 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.

6.8.7 Vital Signs

Vital signs will be summarized overall and by age cohort using descriptive statistics. For each vital sign, the Baseline and final observations (within 28 days of the last dose of eteplirsen) will be presented overall and by age cohort. Additionally, the largest absolute change from Baseline will be summarized. Descriptive statistics will be calculated for the observed values as well as the change from Baseline values.

A table of treatment-emergent markedly abnormal results of vital signs that occur after Baseline as defined in Appendix Table 4 will be generated overall and by age cohort. 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.

6.8.8 Electrocardiograms and Echocardiograms

ECG and ECHO assessments will be summarized overall and by age cohort using descriptive statistics. For each ECG and ECHO parameter, the Baseline and final observations (within 28 days of the last dose of eteplirsen) will be presented overall and by age cohort. Additionally, the largest absolute change will be summarized. Descriptive statistics will be calculated for the observed values as well as the change from Baseline values.

A table of treatment-emergent markedly abnormal results of ECG and ECHO that occur after Baseline as defined in Appendix Table 5 will be generated overall and by age cohort. 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.

6.8.9 Other Safety Assessments

Treatment-emergent markedly abnormal physical examination results will be summarized overall and by age cohort. Abnormal physical exam findings related to neurological and musculoskeletal system, related to DMD, occurred during Screening and Baseline visit, or showing no change from Baseline/Screening will be excluded.

All physical examination, unintended therapeutic benefits, and procedures will be listed.

6.9. [redacted]

[redacted]

[redacted]

6.10. Pharmacokinetic Analyses

For only Study 4658-102, results of all PK analyses will be provided as a separate PK report which will be appended to the final clinical study report (CSR) and summarized in the CSR.

Pharmacokinetic parameters of eteplirsen will be determined from plasma and urine concentration data. Individual plasma and urine levels of eteplirsen will be listed with the corresponding time relative to eteplirsen administration, and summary statistics will be generated by per-protocol time of collection. PK parameters for eteplirsen will be calculated using non-compartmental analysis and/or using population PK methodology, as appropriate. Actual sampling times will be used in all final PK analyses; per-protocol times will be used to calculate mean plasma concentrations for graphical displays.

Plasma and urine concentrations will be listed. PK parameters in plasma and urine will be summarized by dose level and age cohort. Plasma concentrations will be plotted versus elapsed time for dose level means and for individual patients. Dose proportionality will be evaluated across the range of doses studied.

7. CHANGES IN PLANNED ANALYSES

7.1. Changes from Clinical Protocol-Planned Analyses

Compared to the clinical protocol of 4658-102 (Version 4, dated 07 February 2020) [redacted] the interim analysis 4658-102 is removed. There are no other changes in this SAP.

7.2. Changes from Previous Statistical Analysis Plans

Not applicable.

8. APPENDIX

8.1. Criteria of Abnormalities

8.1.1 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	> ULN
Calcium[a]	mmol/L	0.30	0.30	NA
AST (SGOT)	U/L	NA	NA	Value ≥ 2× Baseline Value
ALT (SGPT)	U/L	NA	NA	Value ≥ 2× Baseline Value
Gamma Glutamyl Transferase	U/L	NA	NA	Value > 3× Baseline or > ULN
Alkaline phosphatase	U/L	NA	NA	Value > 1.5× ULN
Albumin	g/dL	1	1	< LLN or > ULN
Total bilirubin[b]	µmol/L	NA	10	Value > 1.5× ULN
Creatine phosphokinase	U/L	NA	NA	Value ≥ 2× Baseline Value
Cystatin C	mg/L	NA	NA	> ULN

[a]multiply mg/dL value by 0.25

[b]multiply mg/dL value by 17.1

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

8.1.2 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

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

8.1.3 Appendix Table 3. Urinalysis Laboratory Abnormalities of Interest

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

8.1.4 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 from Baseline	

8.1.5 Appendix Table 5. Electrocardiogram and Echocardiogram Abnormalities of Interest

Variable	Units	LLN	ULN	Age Group (years)	Markedly Abnormal Criteria
Heart Rate	beats/min	60	130		NA
QTcF Interval	msec	NA	NA	< 12	> 480
				All	< 320 Increase > 60 > 450 > 480 > 500
QRS Interval	msec	NA	NA	< 12	Intraventricular conduction delay (IVCD) or any QRS conduction disturbance with a QRS > 110 msec
PR Interval	msec	NA	NA	< 12	> 190
LVEF	%	NA	NA	All	< 55%
Fractional Shortening	%	NA	NA	All	< 29%

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

Signature: [redacted]

Email: [redacted]

Title: [redacted]

Company: Sarepta Therapeutics Inc

Signature: [redacted]

Email: [redacted]

Title: [redacted]

Company: Sarepta Therapeutics Inc

Signature: [redacted]

Email: [redacted]

Title: [redacted]

Company: Sarepta Therapeutics Inc

Signature: [redacted]

Email: [redacted]

Title: [redacted]

Company: Sarepta Therapeutics Inc

Signature: [redacted]

Email: [redacted]

Title: [redacted]

Company: PharPoint Research, Inc