
# STATISTICAL ANALYSIS PLAN

## Protocol 4658-204

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

(Protocol Version: Amendment 1, 05 July 2016)

| | |
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# 1. INTRODUCTION

This analysis plan summarizes the planned analyses and presentation of the safety and efficacy data from the Sarepta Therapeutics, Inc. Protocol 4658-204: "An Open-Label, Multi-Center Study to Evaluate the Safety and Tolerability of eteplirsen in Patients with Advanced Stage Duchenne Muscular Dystrophy".

The investigational product is eteplirsen injection. Eteplirsen 30 mg/kg will be administered as an intravenous (IV) infusion over approximately 35 to 60 minutes, or approximately 5 mL/min, once a week for up to 96 weeks, followed by a safety extension (not to exceed 48 weeks), until the product is commercially available or until patients can transition into another eteplirsen trial.

# 2. STUDY OBJECTIVES

The primary objective of this study is to explore safety and tolerability of eteplirsen in patients with advanced stage Duchenne muscular dystrophy (DMD) who are amenable to exon 51 skipping.

CCI

# 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Expanded Term |
|---|---|
| CCI | [redacted] |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| DMD | Duchenne muscular dystrophy |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| eCRF | electronic case report form |
| CCI | [redacted] |
| CCI | [redacted] |
| GGT | gamma-glutamyl transferase |
| IV | intravenous |
| KIM-1 | kidney injury molecule-1 |
| LLN | lower limit of normal |
| CCI | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| CCI | [redacted] |
| CCI | [redacted] |
| CCI | [redacted] |
| CCI | [redacted] |
| CCI | [redacted] |
| CCI | [redacted] |
| PT | Preferred Term |
| CCI | [redacted] |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |

| | |
|---|---|
| SD | standard deviation |
| SE | standard error |
| SMQ | standard MedDRA query |
| SOC | System Organ Class |
| CCI | [redacted] |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| ULN | upper limit of normal |
| WHO | World Health Organization |
| CCI | [redacted] |

# 4. STUDY OVERVIEW

## 4.1. Study Design

This is an open-label, multi-center study to explore the safety and tolerability of eteplirsen injection in patients with advanced stage DMD with confirmed genetic mutations amenable to treatment by exon 51 skipping.

Patients will be evaluated for inclusion during a Screening/Baseline period of up to 4 weeks. Eligible patients will receive once weekly IV infusions of 30 mg/kg eteplirsen for up to 96 weeks. An extension period may be considered after the end of the 96-week planned dosing period.

Safety will be regularly assessed throughout the study via the collection of adverse events (AEs), laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations. CCI

## 4.2. Number of Study Sites

This study will be conducted at approximately 10 sites in the United States.

## 4.3. Overall Time and Events Schedule

The Schedule of Events is displayed in Tables 1 and 2. Greater detail concerning the schedule of events can be found in the protocol.

**Table 1 Schedule of Events - Screening to End of Study**

| Study Period | Screening | Treatment Period | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **up to Week -4** | **BL/1** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | X | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | |
| Full Physical Exam | X | X | X | | X | | | X | | | | | | X |
| Brief Physical Exam | | | | X | | X | X | | | | X | | | |
| Vital Signs[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Safety Lab Assessments | X | X[b] | X | X | X | | | X | | | X | | | X |
| CCI [redacted] | [redacted] | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] |
| Whole Blood (Genotyping/CCI)[c] | X | | | | | | | | | | | | | |
| Height and Ulnar Length | X | X | | | X | | | X | | | X | | | X |
| CCI [redacted] | [redacted] | | | | | | | | | | | | | |
| CCI [redacted] | [redacted] | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] |
| ECG | X[f] | | | | X | | | X | | | X | | | X |
| Holter ECG | X[f] | | | | | | | | | | | | | X |
| ECHO | X[f] | | | | X | | | X | | | X | | | X |

| Study Period | Screening | Treatment Period | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **up to Week -4** | **BL/1** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** |
| Study Drug Infusion | | Once Weekly | | | | | | | | | | | | |
| Conmed/Therapy | Continuous | | | | | | | | | | | | | |
| AE Assessment | Continuous | | | | | | | | | | | | | |

**Footnotes for Table 1 Schedule of Events: Screening through Week 48**

Functional assessments, CCI , ECG, Holter ECG, and ECHO have a ±2 weeks window

[a] For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be collected only 30 minutes after the end of the infusion.

[b] Blood samples for the safety laboratory assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1. If more than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, it must be repeated. If less than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, additional safety laboratory assessments do not need to be performed.

[c] Patients may start dosing based on local genotyping results provided that these results fulfill the required inclusion criteria; however, all patients must undergo genetic testing to confirm the exon 51 skippable mutation CCI .

[d] CCI .

[f] Screening ECG, Holter ECG, and ECHO may be performed at any time during the Screening period; however results must be available on Day 1, prior to dosing.

[g] In the event of early termination prior to Week 96, the Week 96 assessments should be completed as the Early Termination Visit.

[h] End of Study visit should occur within 4 weeks after last dose

| **Study Period** | **Treatment Period** | | | | | | | | | | | | **Safety Extension** | **End of Study[h]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **52** | **56** | **60** | **64** | **68** | **72** | **76** | **80** | **84** | **88** | **92** | **96/ET[g]** | **See Table 2** | **4 weeks after last infusion (as applicable)** |
| Informed Consent | | | | | | | | | | | | | | |
| Inclusion/Exclusion | | | | | | | | | | | | | | |
| Medical History | | | | | | | | | | | | | | |
| Full Physical Exam | | | | | | X | | | | | | X | | X |
| Brief Physical Exam | | | | | | | | | | | | | | |
| Vital Signs[a] | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Safety Lab Assessments[b] | | | | | | X | | | | | | X | | X |
| CCI | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| Whole Blood (Genotyping/CCI )[c] | | | | | | | | | | | | | | |
| Height and Ulnar Length | | | | | | X | | | | | | X | | |
| CCI | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| ECG | | | | | | X | | | | | | X | | |
| Holter ECG | | | | | | | | | | | | X | | |
| ECHO | | | | | | X | | | | | | X | | |
| Study Drug Infusion | Once Weekly | | | | | | | | | | | | | |

| Study Period | Treatment Period | | | | | | | | | | | | Safety Extension | End of Study[h] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | 52 | 56 | 60 | 64 | 68 | 72 | 76 | 80 | 84 | 88 | 92 | 96/ET[g] | See Table 2 | 4 weeks after last infusion (as applicable) |
| Conmed/Therapy | Continuous | | | | | | | | | | | | | |
| AE Assessment | Continuous | | | | | | | | | | | | | |

**Footnotes for Table 1 Schedule of Events: Week 52 through End of Study**

Functional assessments, CCI , ECG, Holter ECG, and ECHO have a ± 2 weeks window

[a] For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after the first year of treatment, vital signs may be collected only 30 minutes after the end of the infusion.

[b] Blood samples for the safety laboratory assessments must be obtained within 2 weeks prior to the Baseline/Week 1 visit, and results must be available prior to dosing at Baseline/Week 1. If more than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, it must be repeated. If less than 2 weeks have elapsed since the collection of blood samples for the Screening safety laboratory assessments, additional safety laboratory assessments do not need to be performed.

[c] Patients may start dosing based on local genotyping results provided that these results fulfill the required inclusion criteria; however, all patients must undergo genetic testing to confirm the exon 51 skippable mutation CCI [redacted].

[d] CCI [redacted].

[f] Screening ECG, Holter ECG, and ECHO may be performed at any time during the Screening period; however results must be available on Day 1, prior to dosing.

[g] In the event of early termination prior to Week 96, the Week 96 assessments should be completed as the Early Termination visit.

[h] End of Study visit should occur within 4 weeks after last dose

**Table 2 Schedule of Events - Safety Extension Period**

| **Study Period** | **Safety Extension Period (Starting at Week 97 and continuing until the product is commercially available or until patients can transition into a separate eteplirsen study)** | |
|---|---|---|
| **Week** | **120** | **144** |
| Full Physical Exam | X | X |
| Vital Signs[a] | Weekly | |
| Weight | Every 4 Weeks | |
| Safety Lab Assessments | X | X |
| CCI [redacted] | [redacted] | [redacted] |
| CCI [redacted] | [redacted] | [redacted] |
| ECG | X | X |
| ECHO | X | X |
| Study Drug Infusion | Once Weekly | |
| Conmed/Therapy | Continuous | |
| AE Assessment | Continuous | |

Functional assessments, CCI [redacted], ECG, Holter ECG, and ECHO have a ±2 weeks window

[a] For infusion visits during the Safety Extension Period, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction in the past year of treatment, vital signs may be collected only 30 minutes after the end of the infusion.

## 4.4. Analysis Variables

### 4.4.1 Subject Disposition

- Subjects not completing the study.
- Study drug exposure. This will be characterized by calculating, for each subject, the total amount of medication received during the study and the time in days between the first dose and the last dose.

### 4.4.2 Demographics and Baseline Characteristics

- Age, race, ethnicity, weight, height, body mass index (BMI), genotype for CCI [redacted] CCI [redacted], ambulatory status, and CCI [redacted] will be summarized.
- Age will be calculated at date of first dose of eteplirsen at the Week 1 visit
- For the purposes of the demographic summaries, weight will be the last available measurement taken before the first study drug administration.
- BMI will be calculated as BMI = Weight (kg) / Height $(m)^2$. Any measurements in other units will be converted to kilograms and meters prior to the calculation. Weight (kg) = weight (lb)/2.2. Height (m) = height (inches)*0.0254.

### 4.4.3 Prior and Concomitant Medication

A prior medication is any medication taken prior to the first study drug administration. A concomitant medication is any medication that is taken after the first study drug administration. Prior and concomitant medications will be coded using the current version of the World Health Organization classification for therapeutic class and drug name (WHO Drug Dictionary Enhanced).

### 4.4.4 Efficacy Variables

CCI [redacted]

CCI

[redacted]

### 4.4.5 Safety Variables

The safety and tolerability of eteplirsen will be assessed through:

- A review and evaluation of the frequency and severity of AEs, serious adverse events (SAEs), and discontinuations due to AEs. Adverse events are coded using MedDRA (version 17.1) and are reported by the primary System Organ Class (SOC) and Preferred Term (PT) Name.

  Adverse events will be classified as treatment-emergent AEs (TEAE) and non-treatment-emergent AEs. TEAEs are those events that develop or worsen during the on-treatment period through 28 days after the last dose of eteplirsen. Non-emergent AEs are those that develop during the pre-treatment period or greater than 28 days after treatment completion.

- Safety laboratory tests (hematology, coagulation, serum chemistry assays and urinalysis, including kidney injury molecule-1 [KIM-1]).
- Vital signs.
- Physical examinations.
- 12-lead electrocardiograms.
- Echocardiogram.

## 4.5. Randomization and Blinding

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

# 5. STATISTICAL METHODS

## 5.1. Sample Size

There is no formal sample size calculation. The sample size is based on qualitative considerations and is sufficient to provide safety evaluation of eteplirsen in the studied population. Approximately 20 patients will be enrolled in this study.

## 5.2. Analysis Population

### 5.2.1 Safety Population

The safety population will include all subjects who received at least one dose of eteplirsen.

## 5.3. Handling of Missing Data

Imputation of missing data will not be performed unless otherwise specified. Descriptive statistics will be based upon reported data.

## 5.4. Conventions

### 5.4.1 Covariates

Analyses will not be adjusted for covariates.

### 5.4.2 Multiple Testing

No adjustment for multiple comparisons will be applied. CCI [redacted]

CCI [redacted]

### 5.4.4 Imputation of Incomplete Dates for Concomitant Medications and Adverse Events

An incomplete date occurs when the exact date at which an event occurred or ended cannot be obtained from a subject. Incomplete dates will be imputed as follows:

- For partial or missing medication dates, the medication will be classified as a concomitant medication unless the available part of the date indicates it is not possible 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 would be classified as a prior medication.

  For partial or missing adverse event dates, the event will be classified as treatment-emergent if the month and/or year are on or after the initiation of eteplirsen and within 28 days of the last dose of eteplirsen, or if it is not possible to determine whether the adverse event date is on or after the initiation of eteplirsen and within 28 days of the last dose of eteplirsen.

- For the purpose of calculating the duration of an adverse event with a missing day but known month and year, the first of the month will be used for all start dates and the end of the month will be used for all end dates (where applicable). For example 01MMMYYYY will be used for UNMMYYYY for start date and 31JANYYYY for UNJANYYYY (actual value will be based on the month recorded).

### 5.4.5 Presentations Over Time

For endpoints that are collected serially over time (i.e. laboratory tests, efficacy assessments), events will be assigned to a time-point based upon the eCRF page the event was reported on (nominal time).

### 5.4.6 Definitions and Terminology

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

Study Day 1
Day 1 is defined as the date of first dose of eteplirsen at the Week 1 visit during the 4658-204 Study.

Days on Study
Days on Study is the number of days from Study Day 1 to the date of study completion or early termination as recorded on the END OF STUDY VISIT CRF.

Days on Study Drug
Days on Study Drug is the number of days from the date of first dose to the date of the last dose of the specific study medication as recorded on the STUDY DRUG ADMINISTRATION CRF.

Planned Number of Infusions
The planned number of infusions will be based on the subject's last local site visit. The subject will be expected to receive an infusion once weekly up until their last local site

visit. If a subjects completes 100 local site visits and then completes or discontinues the study the planned number of infusions will be 100.

Treatment Group
All subjects received 30 mg/kg weekly of eteplirsen and will be analyzed in the same group.

Time Since DMD Diagnosis
The time since DMD diagnosis, in months, will be calculated as Month and Year of first dose – Month and Year of diagnosis

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Treatment-Emergent Adverse Event
An AE is considered treatment-emergent if it occurs on or after the initiation of the first dose of eteplirsen and within 28 days of last dose.

Treatment Related Adverse Event
A treatment-related AE is any adverse event reported on the CRF that is marked as definitely, probably or possibly related to study drug. Additionally, it is assumed that an AE without a relationship is treatment-related.

Treatment-Emergent Laboratory Abnormality
A treatment-emergent laboratory abnormality is defined as any laboratory abnormality (as defined in section 5.5.7.2) that occurs following the initiation of eteplirsen which was not present at Baseline.

Prior Medication
A prior medication is any medication taken prior to the first study drug administration.

Concomitant Medication

A concomitant medication is any medication that is taken on or after the first study drug administration.

CCI [redacted]

### 5.4.7 Timing of Analyses

Safety Analyses

Periodic safety analyses were performed during the course of this study. CCI [redacted]

Final Analyses

An analysis will be performed once all subjects complete their End of Study visit and the resulting clinical database has been cleaned, quality checked and locked through the data cut.

### 5.4.8 Programming Conventions

This section details general conventions to be used for the statistical analyses. Departures from these general conventions will be specified in appropriate sections.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD) or as appropriate the standard error of the mean (SE), minimum, and maximum values for continuous variables.
- All mean and median values will be formatted to a precision of 1 more decimal place than the measured value on the electronic case report form (eCRF). Standard deviation (SD) and SE values will be formatted to a precision of 2 more decimal places than the measured value on the eCRF. Minimum and maximum values will be presented with the same precision as the measured value on the eCRF. Percentages will be presented to a precision of 1 decimal place.
- The number and percentage of responses will be presented in the form XX (XX), where the percentage is in the parentheses. Unless otherwise specified, the

denominator for percentages will be the number of subjects in a given treatment group within the analysis population of interest.

- Study day will appear in the data listings as appropriate.
- Date variables will be formatted as DDMMYYYY for presentation. In the case of missing day, month, and/or year information, "UN" will be presented. For example, a date with a missing month and day will be presented as UNUNYYYY.
- Adverse events (AEs) 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.
- Tables, figures, and listings will be presented in landscape orientation.
- P-values will be reported as two-sided p-values. If a p-value is less than 0.001 it will be reported as <0.001.
- SAS® Version 9.2 or higher will be the statistical software package used for all data analysis.

## 5.5. Statistical Analyses

### 5.5.1 Subject Disposition

Subject disposition will be summarized with frequency count and percentage for the following items: subjects who received the study medication (safety population), subjects who completed the study through 96 weeks, and subjects who discontinued early. The reasons for discontinuation will be summarized for all enrolled subjects.

Subject disposition and subject eligibility (including inclusion/exclusion criteria) will be presented in data listings.

### 5.5.1 Demographics and Baseline Characteristics

Demographic characteristics including age (years), race, ethnicity, and Baseline characteristics including genetic mutation, ambulatory status, CCI [redacted], CCI CCI [redacted], height (cm), and weight (kg) will be summarized. Demographic data and Baseline characteristics will be presented in the data listings.

### 5.5.2 Prior and Concomitant Medications

Concomitant medications will be summarized by displaying the number and percentage of subjects with each drug classification and preferred term. All medications, whether prior or concomitant, will appear in the data listings.

### 5.5.3 Medical History

Medical history data will be presented in the data listings.

### 5.5.4 Protocol Deviations

A listing and summary of protocol deviations will be provided.

### 5.5.5 Dosing

The cumulative exposure (mg), total volume of drug administered (mL), total number of infusions received, total number of infusions planned and compliance (calculated as 100*number of infusions received/number of infusions planned) will be summarized. Dosing information will be provided in a data listing.

### 5.5.6 Efficacy

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]


### 5.5.7 Safety

Safety analyses will be descriptive in nature.

#### 5.5.7.1. Adverse Events

Adverse events will be mapped to MedDRA v17.1 preferred terms (PT) and system organ classifications (SOC). Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in the frequency tables. All adverse event tables will be summarized by Baseline ambulatory status and overall. If a subject experiences multiple episodes of the same event with a different relationship/severity, the event with the strongest relationship or maximum severity to the study drug will be used to summarize the AEs by relationship and severity.

Only treatment-emergent adverse events (TEAEs) will be summarized. Non-emergent events will be included in the subject listings. TEAEs and treatment-related TEAEs will be summarized by SOC, PT, and severity. Additionally, serious AEs (SAEs), regardless of their treatment-emergent status, will be summarized by SOC and PT. The following listings will be produced:

1) All AEs
2) Moderate and Severe AEs
3) Treatment-Related AEs
4) SAEs

5) AEs leading to discontinuation

#### 5.5.7.1.1. Adverse Events of Special Interest

Summaries of TEAEs of special interest (AESIs) and other AEs of Interest will be summarized by SOC and PT. All SMQs listed below will include broad and narrow terms. The AESIs are:

- Hypersensitivity (Anaphylactic Reaction SMQ and Anaphylactic/Anaphylactoid Shock Conditions SMQ)
- Renal Toxicity (Acute Renal Failure SMQ)
- Leukopenia and Neutropenia (Haematopoietic SMQ)
- Infusion Site Reactions (Extravasation Events SMQ and the following PTs: Application Site Erythema, Application Site Rash, Catheter Site Haematoma, Catheter Site Haemorrhage, Catheter Site Related Reaction, Infusion Site Rash, Infusion Site Swelling)
- Severe Cutaneous Adverse Reactions (Severe Cutaneous Adverse Reactions SMQ)
- Infusion Related Reactions (PTs of Nausea, Vomiting, Pyrexia, Body Temperature Increased, Erythema, Flushing Infusion Related Reaction, Hypotension, Blood Pressure Decreased, Diastolic Hypotension, Orthostatic Hypotension, Procedural Hypotension, Blood Pressure Ambulatory Decreased, Blood Pressure Diastolic Decreased, Blood Pressure Orthostatic Decreased, Blood Pressure Systolic Decreased, Blood Pressure Systolic Inspiratory Decreased)
- Drug Induced Hepatotoxicities (Cholestasis and Jaundice of Hepatic Origin SMQ, Hepatic Failure, Fibrosis and Cirrhosis and Other Liver Damage-Related Conditions SMQ, Hepatitis, Non-infectious SMQ, Liver Neoplasms, Benign (incl Cysts and Polyps) SMQ, Liver Malignant Tumours SMQ, Liver Tumours 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, Signs and Symptoms SMQ)
- Coagulopathy (Haemorrhage Terms (excluding lab terms) SMQ, Haemotopoietic Thrombocytopenia SMQ, PTs in the Embolism and Thrombosis High Level Group Terms (HLGT)

The Other AEs of Interest are:

- Port-Related Events$^{+}$ (Embolic and Thrombotic Events, Venous SMQ, Extravasation Events (Injections, Infusions and Implants) SMQ, PTs in the following High Level Terms (HLTs): Sepsis, Viraemia and Fungaemia NEC, Implant and Catheter Site Reactions, PTs in the following HLGTs: Endocardial Disorders and Device Issues. In addition, a search will be performed on the verbatim terms for “port”, “central venous” and “central line”)

- Fractures (PTs in the following HLGTs: Fractures and Bone and Joint Injuries)
- Falls (search of verbatim terms for "fall")

+ For subjects who have a port, Port-Related Events will only be identified after the port insertion occurred.

A corresponding listing will be generated for each table.

### 5.5.7.2. Laboratory Measurements

Descriptive statistics for continuous hematology, clinical chemistry, urinalysis, and coagulation laboratory measurements will be presented by time point. Summary statistics for each lab parameter and time point as well as the change from Baseline to the time point will be displayed. For each numeric laboratory parameter, box plots of values over time will be generated. A shift table will compare N (%) of low, normal, and high status of the lab values at Baseline to their worst value post-Baseline through Week 96. A table summarizing the frequency and percent of subjects meeting the predefined markedly abnormal criteria at each visit will be presented. The predefined markedly abnormal criteria are defined below in Tables 3-1, 3-2, and 3-3. All laboratory values will be displayed in a data listing.

**Table 3-1 Predefined Markedly Abnormal Hematology Laboratory Values**

| Test | Unit | Markedly Abnormal Criteria |
|---|---|---|
| Hematocrit | 1 | < LLN |
| Hemoglobin | g/L (or mmol/L) | < LLN |
| Red blood cell count | T/L | < LLN |
| White blood cell count | count/L | >1.5 × ULN or < LLN |
| Platelet count | 10^3/L | < 150 or < 200 with a decrease of at least 100 |
| Basophils (abs) | count/L | > ULN or < LLN |
| Eosinophils (abs) | count/L | > 1.5xULN or < LLN |
| Lymphocytes (abs) | count/L | < LLN |
| Monocytes (abs) | count/L | < LLN |
| Neutrophils (abs) | count/L | >1.5 × ULN or < 1000 |

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

**Table 3-2 Predefined Markedly Abnormal Chemistry Laboratory Values**

| Test | Unit | Predefined Change | | Markedly Abnormal Criteria |
|---|---|---|---|---|
| | | Decrease | Increase | |
| Fasting blood glucose* | mmol/L | 3.1 | 3.2 | |
| Urea (BUN) | mmol/L | | | Value >1.5 × Baseline Value AND > ULN |
| Creatinine | μmol/L | | 35 | Value >1.5 × ULN |
| Sodium | mmol/L | 8 | 8 | |
| Potassium | mmol/L | 1.1 | 1.0 | Value >5.5 mmol/L or < 3 mmol/L |
| Chloride | mmol/L | 9 | 8 | |
| Uric acid | μmol/L | | | >1 × ULN |
| Calcium[#] | mmol/L | 0.30 | 0.30 | |
| Total cholesterol | mmol/L | | 1.73 | |
| AST (SGOT) | U/L | | | Value ≥3 × Baseline Value |
| ALT (SGPT) | U/L | | | Value ≥2 × Baseline Value |
| Gamma GT (GGT) | U/L | | | Value >3 × Baseline Value OR > ULN |
| Alkaline phosphatase | U/L | | | Value >1.5 × ULN |
| Total protein[@] | g/L | 11 | 10 | |
| Albumin | g/dL | 1 g/dL decrease or | 1 g/dL increase | Value < LLN or > ULN |
| Total bilirubin[&] | μmol/L | | 10 | Value >1.5 × ULN |
| LDH | U/L | | | Value ≥2 × Baseline Value |
| Creatine phosphokinase | U/L | | | Value ≥2 × Baseline Value |
| Triglycerides | mmol/L | | 2.88 | |
| Cystatin C | mg/L | | | > ULN |

*Convert to SI unit by multiplying mg/dL value by 0.0555; [#]multiply mg/dL value by 0.25; [@]multiply g/dL value by 10; [&]multiply mg/dL value by 17.1.
TEMA = treatment-emergent markedly abnormal
LLN = lower limit of normal
ULN = upper limit of normal

**Table 3-3 Predefined Markedly Abnormal Urinalysis Laboratory Values**

| Test | Predefined Change | | Markedly Abnormal Criteria |
|---|---|---|---|
| | Decrease | Increase | |
| Protein in urine | | | >1+ |
| KIM-1* | | | > ULN |

* Adult normal ranges provided by the laboratory will be used for all subjects as no pediatric ranges are available.

### 5.5.7.3. Vital Signs

Vital sign parameters will be presented by time point, summarizing the actual values and change from Baseline to each on-treatment time point using descriptive statistics. A table summarizing the frequency and percent of subjects meeting the predefined markedly abnormal criteria at each visit will be presented. The predefined markedly abnormal criteria are defined below in Table 4. Vital signs data will be presented in the data listings.

**Table 4 Predefined Markedly Abnormal Vital Sign Values**

| Variable | Units | Markedly Abnormal Criteria Lower limit | Markedly Abnormal Criteria Upper limit |
|---|---|---|---|
| Systolic blood pressure | mm Hg | <80 | >130 |
| Diastolic blood pressure | mm Hg | <40 | >90 |
| Pulse Rate | beats/min | <50 | >130 |
| Temperature | $^{o}$C | | ≥40 |

### 5.5.7.4. 12-Lead ECGs

Electrocardiogram (ECG) parameters will be presented by time point, summarizing the actual values and change from Baseline to each on-treatment time point using descriptive statistics. A shift table will compare N (%) of ECG status at Baseline to the worst reported value through Week 96. A table summarizing the frequency and percent of subjects meeting the predefined markedly abnormal criteria at each visit will be presented. The predefined markedly abnormal criteria are defined below in Table 5. ECG data will be provided in a data listing.

**Table 5 Predefined Markedly Abnormal Electrocardiogram Values**

| Variable | Units | Lower limit of normal | Upper limit of normal | Age Group (yrs) | Markedly Abnormal Criteria |
|---|---|---|---|---|---|
| Heart Rate | beats/min | 50 | 120 | | |
| QTcF Interval | msec | | | All | Screening Visit >450 |
| | | | | <12 | >480 |
| | | | | ≥12 | >500 |
| | | | | All | <320<br>Increase >60 |
| QRS Interval | msec | | | <12 | IVCD or any QRS conduction disturbance<br>with a QRS >110ms |
| | | | | ≥12 | IVCD or any QRS conduction disturbance<br>with a QRS >120ms |
| PR Interval | msec | | | <12 | >190 |
| | | | | ≥12 | >220 |

### 5.5.7.5. Echocardiograms

The actual value and change from Baseline to each on-treatment time point will be summarized for each ECHO parameter. A table summarizing the frequency and percent of subjects meeting the predefined markedly abnormal criteria at each visit will be presented. The predefined markedly abnormal criteria are defined below in Table 6. ECHO parameters will be listed by subject in a data listing.

**Table 6 Predefined Markedly Abnormal Echocardiography Values**

| Variable | Units | Markedly Abnormal Criteria |
|---|---|---|
| LVEF | % | <55% |
| Fractional Shortening | % | <44% |

### 5.5.7.6. Holter Monitoring

Holter monitoring data will be provided in a data listing. A separate listing will be created for hourly values and summary values.

### 5.5.7.7. Physical Examinations

Physical examination results will be listed by subject in a data listing.

# 6. CHANGES FROM PLANNED ANALYSES

This SAP has made the following change to the planned analyses in the protocol (Amendment 1, 05 July 2016):

- Holter monitoring was to be summarized. It will instead be listed only.

# 7. REFERENCES

None.

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CI

## *Tables and Figures*

CCI

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[redacted]

[redacted]

[redacted]

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***Listings***

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