# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **DRUG:** | Eteplirsen (Eteplirsen Injection) |
| **STUDY NUMBER:** | 4658-102-OLE |
| **STUDY TITLE:** | An Open-Label Safety, Tolerability, and Efficacy Study of Eteplirsen in Patients with Duchenne Muscular Dystrophy Who Have Completed Study 4658-102 |
| **EUDRACT Number:** | 2019-000337-39 |
| **SPONSOR:** | Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 |
| **CURRENT VERSION DATE:** | Version 2, 07 February 2020 |
| **PRIOR VERSION DATE:** | Version 1, 01 March 2019 |

## SIGNATURE PAGE FOR SPONSOR

| | |
|---|---|
| **Protocol Title:** | An Open-Label Safety, Tolerability, and Efficacy Study of Eteplirsen in Patients with Duchenne Muscular Dystrophy Who Have Completed Study 4658-102 |
| **Study No:** | 4658-102-OLE |
| **Current Version Date:** | Version 2, 07 February 2020 |

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

- The current risk-benefit evaluation of the investigational product (IP).
- The ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312; and the European Clinical Trial Directive 2001/20/EC and European Union (EU) Clinical Practice Directive 2005/28/EC; ICH E6 (R2) Good Clinical Practice Guideline.

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

PPD

PPD

PPD

Date

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

## INVESTIGATOR'S AGREEMENT

I have read the Study 4658-102-OLE Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

# PROCEDURES IN CASE OF EMERGENCY

**Table 1: Emergency Contact Information**

| Role in Study | Name and Title | Mailing Address, Telephone Number, and Email Address |
|---|---|---|
| Responsible Physician | PPD | Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>PPD<br>PPD |

# 1. SYNOPSIS

| | |
|---|---|
| **NAME OF COMPANY**<br>Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | **NAME OF FINISHED PRODUCT**<br>Eteplirsen Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>Eteplirsen |
| **TITLE:** An Open-Label Safety, Tolerability, and Efficacy Study of Eteplirsen in Patients with Duchenne Muscular Dystrophy Who Have Completed Study 4658-102 | |
| **Study Number:** 4658-102-OLE | |
| **Phase of Study:** Phase 2 | |
| **INVESTIGATOR STUDY SITES:** This multicenter study will be conducted at approximately 4 sites in Europe. | |
| **OBJECTIVES:**<br>Primary Objective<br>• To evaluate the ongoing safety and tolerability of additional treatment with eteplirsen administered once weekly by intravenous (IV) infusion in male Duchenne muscular dystrophy (DMD) patients who have successfully completed the 96-week eteplirsen study: Study 4658-102.<br>Exploratory Objective<br>• CCI [redacted] | |
| **METHODOLOGY:**<br>This is an open-label extension (OLE) study to assess the ongoing safety, tolerability, and efficacy of weekly IV infusions of eteplirsen in DMD patients who have successfully completed Study 4658-102.<br>Patients will have the opportunity to enroll in this study during the last visit of Study 4658-102 (Week 96).<br>After enrollment, patients will receive the CCI mg/kg dose of eteplirsen while in the study. The period from Baseline through Week 284 will be considered the "Treatment Period."<br>Week 284 will be followed by a 4-week Safety Follow-up Period. Patients may transition to commercially available product if commercially available eteplirsen is available at any time during the study, without undergoing the Safety Follow-up Period. Home infusion of the study drug may be available.<br>Safety and efficacy assessments will be performed at scheduled visits; adverse events (AEs), concomitant medications, and concomitant therapies will be continuously monitored.<br>The CCI [redacted] (CCI [redacted]) will be administered to all patients; a revised version will be used for patients ≤ 3 years of age.<br>If review of data from this OLE study suggests that continued treatment with eteplirsen is warranted, this study may be extended by protocol amendment, or patients may transition to commercially available product if commercially available eteplirsen is available. | |
| **NUMBER OF PATIENTS:** Up to 15 patients will be enrolled in this study. | |

| **NAME OF COMPANY**<br>Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | **NAME OF FINISHED PRODUCT**<br>Eteplirsen Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>Eteplirsen |
|---|---|

**INCLUSION/EXCLUSION CRITERIA:**

**Inclusion Criteria:**

A patient must meet all of the following criteria to be eligible to participate in this study:

1. Patient has successfully completed 96 weeks of treatment in Study 4658-102.
2. Parent(s) or legal guardian(s) who is/are able to understand and comply with the study requirements.
3. Patient and/or their parent(s)/legal guardian(s) are willing and able to provide signed informed consent.

**Exclusion Criteria**

A patient who meets the following criterion will be excluded from this study:

1. Patient has a prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient, or make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results.

**DOSE/ROUTE/REGIMEN(TEST ARTICLE):**

The dose of eteplirsen will be calculated based on the most recent patient weight obtained at the site prior to the current visit. Please refer to the study-specific Pharmacy Manual for information on preparation and administration of eteplirsen.

Patients will receive the CCI mg/kg dose of eteplirsen for up to 284 weeks while in the study.

CCI [redacted] It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, or LMX4 cream) be applied to the infusion site prior to each administration of study drug. Patients should be observed for possible reactions to the infusion for at least 1 hour after each infusion. Home infusion of the study drug may be available.

| **NAME OF COMPANY**<br>Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | **NAME OF FINISHED PRODUCT**<br>Eteplirsen Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>Eteplirsen |
|---|---|
| **REFERENCE TREATMENT:** None | |

**CRITERIA FOR EVALUATION:**

Safety and Tolerability

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 discontinuation of treatment due to AEs
- Deaths due to AEs
- Adverse events of special interest, including infusion-related reactions, hypersensitivity, and renal events
- Laboratory testing, including hematology, coagulation, serum chemistry, and urinalysis
- Cardiac function assessments, including electrocardiogram (ECG)
- Vital signs
- Physical examinations

Efficacy

The efficacy of eteplirsen will be assessed by evaluating the change in NSAA scores from Baseline to the end of Week 144, Week 192, and Week 284.

**STATISTICAL METHODS:**

Sample Size

As this study is an OLE study of Study 4658-102, the sample size will be predicated on the sample size of Study 4658-102.

Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher. An AE will be defined as a treatment-emergent adverse event (TEAE) if it developed or worsened in the period from the first dose of study drug to 28 days after the last dose of study drug. A treatment-related TEAE will be defined as a TEAE that the Investigator considered related to the study treatment.

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | Eteplirsen Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>Eteplirsen |

- **Congenital anomaly/birth defect:** A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the investigational product.
- **Important medical event**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

For TEAEs, treatment-related TEAEs, and treatment-emergent SAEs, the number and percentage of patients reporting AEs will be summarized according to MedDRA system organ class (SOC) and preferred term (PT) for each age cohort and for the overall study. Multiple occurrences of the same AE at the same PT level in the same patient will be counted only once in the calculation of the number and percentage of patients reporting AEs for each PT. In addition, for TEAEs and treatment-related TEAEs, the number and percentage of patients reporting AEs will be summarized, according to MedDRA SOC and PT, by maximum severity for each age cohort and for the overall study. In this summary, if a patient has experienced multiple episodes of the same event with different severities, the event with the maximum severity will be used.

Safety laboratory tests, vital signs, and ECG parameters will be summarized by age cohort and for the overall study using the number and percentage of patients who met the criteria of predefined potentially clinically significant values, as appropriate.

CCI [redacted]

# 2. SCHEDULE OF EVENTS

The schedule of study events is presented in Table 2.

Evaluations should be performed in the order in which they appear below.

On infusion days, all evaluations should be performed prior to infusion, except vital signs, which should be assessed before and after the infusion.

**Table 2: Schedule of Events**

| Weekly Visits | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit/Week** | **BL** | **1[a]** | **12[a]** | **24** | **36** | **48** | **60** | **72** | **84** | **96** | **108** | **120** | **132** | **144** | **156** | **168** | **180** | **192** | **204** | **216** | **228** | **240** | **252** | **264** | **276** | **284 (End of Study[k])** | **288 (Safety Follow-up[l])** |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Eligibility | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Safety Laboratory Assessments[b] | X[c] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Vital Signs[d] | Weekly (pre- and postinfusion) | | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Weight | Weekly | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine dipstick testing | Weekly | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal function blood tests[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Quantitative urine analysis[n] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Physical Exam (including height & ulnar length)[e] | X[c] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| CCI [redacted] [i,o] | X[c,j] | | | | | | | | | X | | | | X | | | | X | | | | | | | | X | |
| ECG[o] | X[c] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Eteplirsen Infusion[f] | Weekly (±3 days after first infusion) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Con Meds/Therapies Assessment | Weekly | | | | | | | | | | | | | | | | | | | | | | | | | | |
| AE Assessment[g,h,i] | Weekly | | | | | | | | | | | | | | | | | | | | | | | | | | |

AE = adverse event; AESI = adverse event of special interest; BL = Baseline; con med = concomitant medication; ECG = electroc ardiogram; EOS = end-of-study; ICF = informed consent form; CCI [redacted] = CCI [redacted]; OLE = open-label extension.

[a] For Weeks 1 to 283, visits will include vital signs, weight, eteplirsen infusion, and assessments of con meds/therapies and AEs. Additionally, the Week 12 visit and visits every 12 weeks subsequently will also include safety labs, ECG, and physical exam (including height and ulnar length).

[b] Safety laboratory assessments will include hematology tests (including platelets), coagulation studies, serum chemistries (in cluding liver function).

[c] These assessments will not be performed at Baseline if performed at Week 96 of Study 4658-102.

[d.] Vital signs will include blood pressure, heart rate, respiration, and axillary temperature. On infusion days, vital signs will be measured within 60 minutes prior to infusion and 30 minutes (± 10 minutes) after the end of the infusion. All assessments will be performed after patients have remained calm for 5 minutes. Pulse rate and respiratory rate should be measured over 1 minute.

[e.] Height and ulnar length will be measured as part of every physical examination. The examination will also include general appearance; head, ears, eyes, nose, throat; heart; lungs; chest; abdomen; skin; lymph nodes; musculoskeletal system; and neurological systems.

[f.] Patients will receive CCI mg/kg of eteplirsen once a week over 35-60 minutes, and will be observed for at least 1 hour after each infusion. It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, or LMX4 cream) be applied to the injection site prior to each infusion.

Once a patient begins receiving weekly eteplirsen infusions at satellite sites, all subsequent infusions should be administered at the patient's satellite site unless otherwise indicated and approved by the Medical Monitor. Patients may receive home infusions starting at Week 1. Note that an implanted venous access port may be inserted for eteplirsen administration at the discretion of the Investigator.

[g.] AEs should be recorded at all visits. Spontaneously reported AEs occurring within 28 days after the last dose of eteplirsen will also be recorded.

[h.] In the event that a patient experiences an AESI of infusion-related reaction, an infusion-related reaction case report form should be completed.

[i.] Special situations (eg, overdose, medication error, accidental/occupational exposure) should be monitored and recorded.

[j.] For patients aged ≤ 3 years the revised CCI will be used. For patients aged >3 age-appropriate items from the CCI (Mercuri 2016) should be performed.

[k.] Patients who are withdrawn from the study early will be asked to complete all end-of-study (EOS) assessments prior to withdrawal and within 28 days of their last eteplirsen infusion, if possible, unless they have completed a physical exam and safety labs within 28 days of withdrawal.

[l.] All patients will be asked to complete the Safety Follow-up visit 28 days after their last dose of eteplirsen. Patients may transition to commercially available product if commercially available eteplirsen is available.

[m.] Renal function blood tests include creatinine, blood urea nitrogen, and serum cystatin C.

[n.] Quantitative urine analysis includes KIM-1 and urinalysis (pH, specific gravity, protein, glucose, ketones, cytology, and hemoglobin).

[o.] A 2-week window is allowed in the event the child is unable to complete this assessment at a given visit.

Note: Rollover Instructions:

- Subject is able to rollover within 1 week (7 calendar days) from main to OLE
  - Main study Week 96 study assessments will be used as Baseline assessments in OLE
  - No safety follow-up visit needed for main study
- Subject rolls over to OLE more than 7 days after conclusion of main study
  - All baseline assessments to be performed fresh for OLE study
  - No safety follow-up visit needed for main study if rollover/ICF for OLE occurs within 4 weeks of main study Week 96
  - If rollover/ICF occurs more than 4 weeks after Week 96 of main study, perform safety follow-up visit

# 3. TABLE OF CONTENTS

# LIST OF TABLES

# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the time-concentration curve |
| BMD | Becker muscular dystrophy |
| CK | creatine kinase |
| CRO | contract research organization |
| CT | Computed tomography |
| DMC | Data Monitoring Committee |
| DMD | Duchenne muscular dystrophy |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| GDPR | General Data Protection Regulations |
| GFR | Glomerular filtration rate |
| GGT | gamma-glutamyl transferase |
| GLDH | Glutamate dehydrogenase |
| HIPAA | Health Insurance Portability and Accountability Act |
| IEC | Independent Ethics Committee |
| INR | International normalized ratio |
| IP | investigational product |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| mRNA | messenger ribonucleic acid |
| CCI | CCI score |
| OLE | open-label extension |
| PMO | phosphorodiamidate morpholino oligomer |

| Abbreviation | Definition |
|---|---|
| PODCI | Pediatric Outcomes Data Collection Instrument |
| PT | preferred term |
| RBC | Red blood cell |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| WHODrug | World Health Organization Drug Dictionary |

# 5. INTRODUCTION

## 5.1. Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare (estimated incidence of 1 in 5,000 live male births; CDC 2009, Emery 1991), degenerative, X-linked, recessive genetic disorder caused by mutations in the dystrophin gene. In DMD, mutations in the dystrophin gene disrupt the open reading frame, resulting in an absence of functional dystrophin, a critically important part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contraction causes cellular degeneration, regeneration, and inflammation, and, over time, myonecrosis.

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

Existing interventions for DMD patients with mutations amenable to exon skipping are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation. Current pharmacologic treatments, such as corticosteroids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function (Beenakker 2005, Biggar 2006, Pradhan 2006). However, their benefits are only temporary, and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, Cushingoid facies and habitus, and cataracts (Biggar 2006, Manzur 2004).

## 5.2. Phosphorodiamidate Morpholino Oligomers for the Treatment of Duchenne Muscular Dystrophy

Ribonucleic acid (RNA) therapeutics are compounds composed of heterocyclic nucleobases (adenine, cytosine, guanine, and thymine, or analogues) linked together on an oligomer backbone that supports hybridization via Watson-Crick base pairing with specific complementary RNA targets. RNA therapeutics can be synthesized to bind targeted RNA sequences in a pathogen or pathogenic process to treat a wide range of diseases through positively or negatively modulating gene expression.

A relatively new use of RNA therapeutics is to target a pre-messenger RNA (mRNA) in the nucleus of a cell to influence the splicing process that creates a mature mRNA. Referred to as "exon skipping," this approach allows determination of which exons will be incorporated into the mature mRNA to be translated into the protein product.

Phosphorodiamidate morpholino oligomers (PMOs) are a class of synthetic molecules based on a redesign of the natural nucleic acid structure. Phosphorodiamidate morpholino oligomers are distinguished from natural nucleic acids and other oligonucleotide therapeutic platforms by the attachment of nucleobases to a 6-membered morpholine ring, as opposed to the 5-membered ribose ring found in RNA and deoxyribonucleic acid (DNA). Moreover, the morpholine rings are linked through neutrally charged phosphorodiamidate moieties, as opposed to negatively charged phosphodiester linkages in RNA and DNA. These differences were designed to increase stability and address safety issues seen with some earlier oligonucleotide backbone chemistries.

Phosphorodiamidate morpholino oligomers are capable of avid, sequence-specific binding in vivo to regulatory sites in pre-mRNA, and thus alter the splicing of a pre-mRNA transcript, such as that of dystrophin, causing the skipping (omission) of specific exons in the final mRNA. Approximately 80% of boys with DMD have out-of-frame deletions that could be amenable to exon-skipping therapies (Aartsma-Rus 2009). Several PMOs are being evaluated by Sarepta Therapeutics, Inc. (hereafter, "the Sponsor") for the potential treatment of DMD, as exon skipping may enable the production of an internally deleted, functional dystrophin protein.

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

## 5.3. Clinical Experience with Eteplirsen

As of 24 June 2019, the eteplirsen clinical development program consists of 7 completed studies (Studies 4658-33, 4658-28, 4658-us-201, 4658-us-202, 4658-203, 4658-301 and 4658-204) and 2 ongoing studies (Studies 4658-102/102 OLE) in patients with DMD who were amenable to Exon 51 skipping. In addition, 2 Phase 1 studies (Studies 4658-101 and 4658-103) have been completed and 1 Phase 1 study (Study 4658-104) is ongoing in volunteers who do not have DMD.

Seven completed studies (Studies 4658-28, 4658-us-201, 4658-us-202, 4658-203, 4658-101, 4658-301 and 4658-103) have contributed to the pharmacokinetic profile of eteplirsen. There was little or no accumulation in plasma following weekly administration. Maximum plasma concentration and area under the concentration-time curve (AUC) increased in an approximately dose-proportional or slightly less than proportional manner. Urinary elimination of the active ingredient without metabolites was the predominant route of excretion. Based on the results of

Study CCI, an increase in eteplirsen exposure was observed in non-DMD adults with mild to moderate renal impairment.

Clinical efficacy results that include ambulatory and pulmonary function have been evaluated in completed Studies 4658-us-201/202, 4658-203, 4658-204 as well as Study 4658-301. Study 4658-us-201/202 provides long-term results across multiple ambulatory and respiratory endpoints over the course of 4 years. Studies 4658-301 (interim analysis) and 4658-204 provide additional supportive evidence of ambulatory and pulmonary function over the course of 2 years. Pooled results from these 3 studies (Studies 4658-us-201/202, 4658-203, and 4658-204) were compared with data from comparable external control cohorts and a comprehensive review of literature describing the natural history of DMD. Results from these analyses demonstrated a divergence, starting at Year 2, favoring eteplirsen-treated patients. Study 4658-301 confirmed mechanism of action showing increasing exon skipping leading to 0.52 % dystrophin levels by Western Blot which significantly & consistently increased over Baseline starting at Week 24 and continuing to Week 96 (n=77). Overall, the long-term safety profile of eteplirsen for treatment of patients with DMD was consistent with previous study data.
Study 4658-203 was a Phase 2, multicenter, open-label trial to evaluate the safety and tolerability of eteplirsen in patients aged 4 to 6 years with genotypically-confirmed DMD with genetic mutations amenable to treatment by exon 51 skipping. The study enrolled 26 patients who received once-weekly intravenous (IV) infusions of CCI mg/kg eteplirsen for up to 96 weeks. Treatment with eteplirsen was well tolerated and safety results were consistent with a favorable safety profile for eteplirsen. Analyses of clinical efficacy endpoints were exploratory in nature: in eteplirsen-treated patients, improvements from Baseline in functional motor abilities and health-related quality of life, Pediatric Outcomes Data Collection Instrument (PODCI) global functioning score, and 10-meter walk/run time were observed.

As of 24 June 2019, 182 patients with DMD and 59 non-DMD subjects have been treated with eteplirsen in clinical studies, including 175 who received IV eteplirsen and 155 who received CCI mg/kg or higher. Of the 182 patients, 17 and 135 patients received at least 48 and 96 weeks of eteplirsen treatment, respectively. This includes 12 patients from Study 201/202 who have been treated for over 5 years. These studies demonstrated that treatment with eteplirsen was generally well-tolerated at doses of CCI mg/kg (N=149) and 50 mg/kg (N=6) and there were no observed difference in safety between these 2 doses.

Based on the cumulative available safety data from these studies, eteplirsen has been shown to be well-tolerated, with low rates of serious or severe adverse events (AEs).

Refer to the eteplirsen Investigator's Brochure for further details.

## 5.4. Rationale for the Current Study

The purpose of this study is to evaluate the ongoing safety and tolerability of additional treatment with eteplirsen, administered once weekly by IV infusion in male DMD patients who have successfully completed the 96-week eteplirsen study: Study 4658-102. This study also plans to evaluate the efficacy of additional treatment with eteplirsen administered once weekly by IV infusion in male DMD patients who successfully completed Study 4658-102.

## 5.5. Benefit and Risk Assessment

Details about the known and expected benefits and risks of, and expected AEs associated with, eteplirsen treatment are provided in the eteplirsen Investigator's Brochure.

Eteplirsen has been granted accelerated approval in the US by the Food and Drug Administration . This was based on the observation of dystrophin production in some patients and the safety experience in patients with DMD participating in clinical trials, who were 4 years of age or older, which includes the age range specified for this study. Patients have also used commercially available eteplirsen since the approval in September 2016.

To date, eteplirsen has been well tolerated, with low rates of serious or severe AEs. No major safety risk has been identified in patients dosed with eteplirsen, including patients dosed with up to 50 mg/kg once weekly for more than 4 years.

Risks with eteplirsen include infusion-related reactions, hypersensitivity reactions, and potential renal toxicities including proteinuria or decreased renal function. These events have been seen in prior experience with eteplirsen with lower doses and are usually mild and resolve without clinical or pharmaceutical treatment. The use of higher doses of eteplirsen in this protocol could lead to more frequent or more severe reactions than seen with lower doses. Regularly scheduled review by a Safety Review Committee during the open-label period and a Data Monitoring Committee (DMC) during the double-blind period will look at aggregate unblinded data to determine the relative risk-benefit of continuing the dose or the study. Investigators are allowed to withhold dosing and must discuss such actions with the Medical Monitor. Further details on the safety of eteplirsen can be found in the Investigator's Brochure.

Based on the mechanism of action of eteplirsen and the benefit of eteplirsen treatment in DMD patients with mutations amenable to skipping exon 51, it is expected that patients in Study 4658-102-OLE may derive a clinical benefit from treatment with a higher dose of eteplirsen.

Taken together, these considerations support that patients participating in Study 4658-102-OLE will not be exposed to undue risk and may potentially experience some clinical benefit.

# 6. STUDY OBJECTIVES AND PURPOSE

## 6.1. Primary Objective

- To evaluate the ongoing safety and tolerability of additional treatment with eteplirsen administered once weekly by IV infusion in male DMD patients who have successfully completed the 96-week eteplirsen study: Study 4658-102.

## 6.2. Exploratory Objective

- CCI

# 7. INVESTIGATIONAL PLAN

## 7.1. Overall Study Design

This is an open-label extension (OLE) study to assess the ongoing safety, tolerability, and efficacy of weekly IV infusions of eteplirsen in DMD patients who have successfully completed Study 4658-102.

Patients will have the opportunity to enroll in this study during the last visit of Study 4658-102 (Week 96). After enrollment, patients will receive the CCI mg/kg dose of eteplirsen while in this study. The period from Baseline through Week 284 will be considered the "Treatment Period."

Week 284 will be followed by a 4-week Safety Follow-up Period. Patients may transition to commercially available product if commercially available eteplirsen is available at any time during the study, without undergoing the Safety Follow-up Period. Home infusion of the study drug may be available.

Safety and efficacy assessments will be performed at scheduled visits; AEs, concomitant medications, and concomitant therapies will be continuously monitored.

CCI [redacted]

If review of data from this OLE study suggests that continued treatment with eteplirsen is warranted, this study may be extended by protocol amendment, or patients may transition to commercially available product if commercially available eteplirsen is available.

Refer to Section 10 for the detailed list of study assessments.

## 7.2. Dose Selection Rationale

Eteplirsen will be dosed weekly at CCI mg/kg over the course of 284 weeks, based upon the dosing scheme utilized in Study 4658-102.

Dose selection for the patient group aged 6 months to 4 years was based on the assumption that efficacy relates to exposure, defined using AUC. The CCI mg/kg dose was chosen as the target dose based on results from the Phase 2, double-blind, placebo-controlled, multiple-dose study, Study 4658-us-201, and its OLE study, Study 4658-us-202. As described in Section 5.3, these studies assessed the efficacy, safety, tolerability, and pharmacokinetics of 2 eteplirsen doses (CCI and CCI mg/kg) administered as IV infusions in 12 patients, aged 7 to 13 years, diagnosed with DMD with a deletion mutation amenable to exon 51 skipping.

As of 24 June 2019, 182 patients with DMD and 59 non-DMD subjects have been treated with eteplirsen in clinical studies, including 175 who received IV eteplirsen and 155 who received CCI mg/kg or higher. Of the 182 patients, 17 and 135 patients received at least 48 and 96 weeks of eteplirsen treatment, respectively. This includes 12 patients from Study 201/202 who have been treated for over 5 years. These studies demonstrated that treatment with eteplirsen was generally well-tolerated at doses of CCI mg/kg (N=149) and 50 mg/kg (N=6) and there were no observed difference in safety between these 2 doses.

In these studies, once-weekly treatment with CCI mg/kg eteplirsen for 24 weeks significantly increased the mean percentage of dystrophin-positive muscle fibers as percentage (%) of normal

in DMD patients compared to placebo. At Week 48, increases in the percentage of dystrophin-positive fibers were similar for patients who had received weekly 30 and 50 mg/kg eteplirsen doses from Week 1 (52% and 42% of normal, respectively, or 47% for the combined groups; data on file). These data suggest that the effect of eteplirsen on the production of novel dystrophin is not significantly different between the 2 doses tested. Therefore, the lower (CCI mg/kg) dose was selected as the more conservative choice, because patients presumably would receive this drug as a lifelong treatment. To date, there is no evidence that the response differs across age groups.

The overall safety data obtained to date do not indicate any significant safety concerns with eteplirsen at doses that are one-third to one-half of the dose in this study. For patient exposure and safety data, please refer to the eteplirsen Investigator's Brochure.

## 7.3. Study Endpoints

### 7.3.1. Safety and Tolerability Endpoints

- Incidence of AEs, serious adverse events (SAEs), and discontinuation from treatment due to AEs
- Incidence of deaths due to AEs
- Incidence of adverse events of special interest (AESIs), including infusion-related reactions, hypersensitivity, and renal events
- Clinically significant laboratory testing, including hematology, coagulation, serum chemistry, and urinalysis
- Clinically significant cardiac function assessments, including electrocardiogram (ECG)
- Clinically significant vital signs
- Clinically significant physical examinations

### 7.3.2. Exploratory Endpoint

CCI [redacted]

## 7.4. Discussion of Study Design

This OLE study focuses on safety and efficacy in male DMD patients who initiated eteplirsen treatment as early as 6 to 48 months of age. CCI [redacted]

No other disease-modifying treatment exists to serve as an appropriate, active comparator for this patient population of boys with DMD aged 6 to 48 months; ataluren is commercially available in the European Union, but is not indicated for use in patients with exon 51-amenable mutations (PTC Therapeutics).

The patients in this study will have an established clinical diagnosis of DMD with a deletion mutation amenable to exon 51 skipping. These are the patients for whom eteplirsen is potentially effective and may result in slowing of disease progression. The age range for the patients in the original study (Study 4658-102) (6 to 48 months old, inclusive) was chosen to establish the safety profile of eteplirsen in this age group.

Patients will have the option to continue to receive once-weekly IV infusions of eteplirsen for up to 284 weeks, in order to obtain safety data in this population. Refer to the eteplirsen Investigator's Brochure for safety information.

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

## 8.1. Number of Patients

Up to 15 patients will be enrolled in this study.

## 8.2. Patient Inclusion Criteria

A patient must meet all of the following criteria to be eligible to participate in this study:

1. Patient has successfully completed 96 weeks of treatment in Study 4658-102.
2. Parent(s) or legal guardian(s) who is/are able to understand and comply with the study requirements.
3. Patient and/or their parent(s)/legal guardian(s) are willing and able to provide signed informed consent.

## 8.3. Patient Exclusion Criteria

A patient who meets the following criterion will be excluded from this study:

1. Patient has a prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient, or make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results.

## 8.4. Completion of a Patient's Participation in the Study

Patients will be considered to have completed participation in this study once the Week 284 assessments have been completed. Patients may continue in the study for a period up to and including 284 weeks, based on the judgement of the Investigator (described further in Section 7.1); however, a Safety Follow-up visit will occur approximately 4 weeks after the last eteplirsen dose administered, regardless of the patient's duration in the study.

The length of a patient's participation will be calculated from the time the informed consent form is signed until completion of the Safety Follow-up visit (approximately 4 weeks after the last dose of eteplirsen is administered).

## 8.5. Completion of the Study

This study will be considered to have been completed upon the last visit of the last patient who had their treatment extended (and the 4-week Safety Follow-up) to Week 288, or transitioned to the commercially available product if available.

## 8.6. Patient Withdrawal Criteria

Any patient can decide to withdraw from study participation at any time for any reason. In addition, the Sponsor may decide to stop the study participation of any patient as deemed necessary. The Investigator may also stop the study participation of any patient at any time.

Reasons for withdrawal from this study include, but are not limited to:

- The patient was erroneously included in the study (ie, was found to not have met the eligibility criteria).
- The patient experiences an intolerable or unacceptable AE.
- The patient is unable to comply with the requirements of the protocol.
- The patient participates in another investigational study without the prior written authorization of the Sponsor.

The Investigator or study staff will document the reason(s) for treatment discontinuation.

Patients who have received at least 1 dose of study treatment and who are withdrawn from treatment within 28 days after a functional assessment visit will be asked to return for an Early Termination (Week 284) visit approximately 28 days after their last dose of eteplirsen. Patients who receive at least 1 dose of study treatment and are withdrawn from treatment more than 28 days after a functional assessment visit will be asked to complete all Early Termination (Week 284) assessments within approximately 28 days after the last dose of eteplirsen.

Patients withdrawn from treatment will not be replaced.

## 8.7. Study Discontinuation

If the Sponsor, the Investigator, the Medical Monitor, the study monitor, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or appropriate regulatory officials discover conditions arising during the study that indicate this study should be halted, or that a study site should be terminated, appropriate action may be taken after consultation among (at a minimum) the Sponsor, the Investigator, the IRB/IEC, and the Medical Monitor.

Conditions that may warrant termination of the study or an individual study site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to comply with pertinent regulations of the IRB/IEC or appropriate regulatory authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, the IRB/IEC, or appropriate regulatory authority
- Insufficient adherence to protocol requirements consistent with the European Clinical Trial Directive 2001/20/EC

# 9. TREATMENT OF PATIENTS

## 9.1. Investigational Product

Eteplirsen drug product is supplied as a sterile, phosphate-buffered saline solution in single-use, 2-mL vials, each containing 2 mL of eteplirsen at 50 mg/mL. The solution is a clear to slightly opalescent and colorless liquid that may contain white to off white particles. Eteplirsen will be administered once a week by IV infusion.

### 9.1.1. Packaging and Labeling

Please refer to the study-specific Pharmacy Manual for information on packaging, labeling, and preparation instructions.

The label text for the IP will, at a minimum, include the following information: product name/identifier, cautionary statement, lot number (or alternative code), storage conditions, and the name of the Sponsor, pursuant to regional requirements.

### 9.1.2. Storage

Vials of IP must be stored in a secured, limited-access area with appropriate temperature recording, controls, and monitoring. Details for storage can be found in the study-specific Pharmacy Manual.

## 9.2. Treatments Administered

Eligible patients will receive a once weekly IV infusion of eteplirsen for up to 284 weeks. Eteplirsen should be prepared for dosing by following the steps detailed in the study-specific Pharmacy Manual.

Patients will receive the CCI mg/kg dose of eteplirsen while in this study. The period from Baseline through Week 284 will be considered the "Treatment Period."

The following guidelines for the timing of dosing should be followed throughout the study:

- Patients should receive eteplirsen once every 7 days starting on Week 1. A window of ±3 days from the scheduled dose is acceptable after the first infusion.
- Patients may not receive two (2) separate doses of eteplirsen within the same 60-hour period.
- The Medical Monitor should be contacted in the event of ≥2 consecutive missed doses.

Week 284 will be followed by a Safety Follow-up Period of up to 4 weeks. Patients may transition to commercially available product if commercially available eteplirsen is available. Home infusion of the study drug may be available.

The administered dose is calculated by patient weight, which will be collected on a weekly basis and used to calculate the dose to be administered at the next visit(s). For example, the weight collected at Week 2 will be used to calculate the doses to be infused during the Week 3 visit. Refer to the Pharmacy Manual for more details on dosing administration.

#### 9.2.1. Dose Modification, Reduction, or Delay

##### 9.2.1.1. Dose Interruption

If a patient experiences an AE that requires interruption of eteplirsen administration for ≥ 2 consecutive doses, the Investigator will consult with the Medical Monitor to determine whether the patient may resume study treatment.

Stopping rules are provided in Section 9.6.

## 9.3. Randomization and Blinding

This is an open-label study, and therefore all patients will receive eteplirsen without blinding.

## 9.4. Prior and Concomitant Medications

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

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

- Previous or current investigational agents (with the exception of drisapersen: patients may be included in the study if they have not received drisapersen for 6 months prior to the Week 1 study dose)
- Immunosuppressants (other than oral or systemic corticosteroids; the corticosteroid should not be administered during the infusion of eteplirsen)
- Previous (within 12 weeks prior to the Week 1 dose) or current systemic aminoglycoside antibiotic or statin

In general, drug therapies that are not excluded per the entry criteria, including over-the-counter medications, may be used before enrollment and throughout the study. However, the number of over-the-counter medications should be limited and the dosage of any such medication should be constant for at least 1 month prior to starting study treatment and throughout the study, unless clinically indicated.

The Investigator should contact the Medical Monitor if unsure about changing a specific medication.

## 9.5. Treatment Compliance

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

## 9.6. Rules for Dose Interruption

The following situations could result in dose interruption of a single patient:

- Any SAE considered to be related to eteplirsen
- See Section 10.3.4 for Safety Monitoring, Additional Investigations and Stopping Rules

If a patient meets one of the above criteria, the study monitor should be immediately notified, and dosing should be suspended until the patient's safety information can be reviewed by the DMC. Dosing may resume only after approval of the DMC, Sponsor, and Investigator, and after approval of a substantial amendment by the competent authority.

Conditions that may warrant interrupting dosing for all patients in the study for additional safety review include, but are not limited to:

- Any SAE of life-threatening or fatal outcome assessed as related by the Investigator
- > 2 patients with severe AEs that result in interruption of individual patient dosing (described earlier in Section 9.6 )
- Any unexplained or drug-related organ failure (eg, liver or renal failure)

The DMC will monitor safety data on an ongoing basis. If the DMC determines that the criteria for study interruption are met, dosing will be suspended until all available patient information related to the event(s) of interest can be reviewed in more detail. Discontinuation of dosing for an individual patient may occur based on the recommendation of the DMC, investigator, the patient, and the local Independent Ethics Committee (IRB/IEC).

# 10. STUDY ASSESSMENTS

## 10.1. Study Schedule of Events

A detailed schedule of the study assessments and time points is shown in Table 2.

## 10.2. Baseline Assessments

### 10.2.1. Informed Consent

Written informed consent from the patient and/or their parent(s)/legal guardian(s) to participate in this study must be obtained prior to beginning any of the procedures for this study.

### 10.2.2. Other Assessments

Baseline assessments will also include clinical safety laboratory assessments, vital signs, physical examination, height/ulnar length, weight, 12-lead ECG, assessment of prior and concomitant medications/therapies, and assessment of AEs.

## 10.3. Safety Assessments

### 10.3.1. Physical Examination

The Investigator or a medically qualified subinvestigator will perform physical examinations at designated study visits, including examination of general appearance; head, ears, eyes, nose, and throat; heart; lungs; chest; abdomen; skin; lymph nodes; musculoskeletal system and neurological system.

### 10.3.2. Vital Signs

Vital signs (blood pressure, heart rate, respiration, and axillary temperature) will be measured at the time points specified in Table 2. Refer to the Study Manual for more details on the methods for obtaining vital signs.

For infusion visits, vital signs are to be collected within approximately 60 minutes prior to infusion and 30 minutes (± 10 minutes) after the end of the infusion. All assessments will be performed after patients have remained calm for 5 minutes. Pulse rate and respiratory rate should be measured over 1 minute.

### 10.3.3. Height/Length and Weight

Height/ulnar length and weight will be measured at the time points specified in Table 2 prior to study drug infusions, to determine the volume of study drug to be administered. Details about how weight measurements are obtained are provided in the Study Manual. If a patient's weight or height/ulnar length varies by more than 10% from the corresponding assessment from the prior visit, the patient should be re-measured or re-weighed to confirm the result, and an explanation of the change should be documented.

Height will be measured at the time points specified in Table 2. Height is to be measured with shoes off. If standing height cannot be obtained, height is to be calculated using the following equation (Gauld 2004):

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

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

Ulnar measurements will be recorded for all patients at each site visit.

### 10.3.4. Safety Monitoring, Additional Investigations and Stopping Rules

#### 10.3.4.1. Safety Monitoring for Liver Chemistry Tests

Liver chemistry tests need to be monitored as specified in the Schedule of Events (Table 2).

Initial abnormal liver chemistry test result(s) needs to be confirmed if:

- Gamma-glutamyl transferase (GGT) or Glutamate dehydrogenase (GLDH) or Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) measurement is > 3 x the upper limit of normal (ULN) (or > 2 x Baseline value if the Baseline value was > ULN) at any time during the study.

Patients with confirmed liver chemistry test results (as above) need to have their liver chemistry tests (GGT, GLDH, ALT, AST, alkaline phosphatase ), international normalized ratio [INR] and total bilirubin) retested 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.

*Additional Investigations:*

Patients with confirmed abnormal liver chemistry test results (as above) are recommended to have the following evaluations performed:

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; Non-Alcoholic SteatoHepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography (CT) or magnetic resonance imaging (MRI) scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.

*Stopping Rules for Liver Test Results:*

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

- GGT or GLDH > 8 x ULN, which is confirmed
- GGT or GLDH > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
- GGT or GLDH > 3 x ULN, which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
- GGT or GLDH > 3 x ULN which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%) felt by the Investigator to be potentially related to hepatic inflammation.

#### 10.3.4.2. Safety Monitoring for Renal Function

Renal tests need to be monitored as specified in the Schedule of Events (Table 2). Patients with the following test results need to undergo repeat testing for confirmation of abnormal test results:

- Protein ≥ 2+ (dipstick)
- Urine Protein to Creatinine Ratio ≥ 150mg/g
- Urine Albumin to Creatinine Ratio ≥ 30mg/g
- Serum Creatinine ≥ 0.3 mg/dL above baseline
- Serum Creatinine ≥ 1.5x ULN
- Estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m$^2$
- Red blood cells (RBCs) > 1/hpf
- Elevated Cystatin C > ULN
- Elevated kidney injury molecule 1 > ULN

*Additional Investigations:*

24-hour urine collection needs to be undertaken to quantify any proteinuria and glomerular filtration rate (GFR) changes indicated by confirmed results as above. Additional evaluations including nephrology consultation, renal US/CT/MRI, renal biopsy, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

*Stopping Rules for Renal Test Results:*

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will be stopped permanently:

- Quantitative total urine protein measurement of ≥ 1 g/24 hours
- Measured GFR (creatinine clearance) ≤ 45 mL/min/1.73m$^2$
- Gross hematuria
- Any RBC Casts
- Persistent microscopic hematuria ≥ 3 RBCs/hpf for 3 consecutive weeks

#### 10.3.4.3. Safety Monitoring for Hypersensitivity

Patients will be monitored for occurrence of allergic reactions primarily via monitoring adverse events as specified in the Schedule of Events (Table 2). Patients will be instructed to promptly report any signs or symptoms of fever or constitutional symptoms that may arise during the study and the Investigator needs to closely evaluate all potential causes, including concomitant illness.

*Additional Investigations:*

Patients who experience significant or persistent constitutional symptoms need to be discussed with the Sponsor Medical Monitor to determine whether additional monitoring or laboratory tests are required. Additional evaluations including immunology consultation, tests for allergic reactions (absolute eosinophils, serum/plasma tryptase), may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

*Stopping Rules for Hypersensitivity AEs:*

In the event of a confirmed hypersensitivity AE meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will have their treatment permanently discontinued.

- Anaphylaxis, anaphylactoid reaction, or angioedema
- Any serious allergic reaction

#### 10.3.4.4. Safety Monitoring for Platelet Count Results

The platelet count needs to be monitored as specified in the Schedule of Events (Table 2).

Patients who have a confirmed occurrence of platelets < 75,000/ $mm^3$ need to have the following evaluations performed:

- Complete blood count with reticulocytes
- Peripheral blood smear
- Coagulation panel (prothrombin time /INR, activated partial thromboplastin time )
- High-sensitivity C-reactive protein

*Additional Investigations:*

Additional platelet evaluations for confirmed, unexplained significant platelet count reductions, including hematology consultation, fibrinogen, fibrinogen split products/D-dimer, von Willebrand factor, total immunoglobulins, complement levels, viral serologies, auto-antibody screen, antiplatelet antibodies and anti-PF4 assay, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

*Stopping Rules for Platelet Test Results:*

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with eteplirsen will be stopped permanently:

- Platelet count < 50,000/$mm^3$

***Safety Monitoring for Rhabdomyolysis***

Rhabdomyolysis must be monitored by urine dipstick and adverse events as specified in the Schedule of Events (Table 2).

- Patients who have confirmed heme+ dipstick urinalysis need to be evaluated for urine microscopy and the following AEs:
- Rhabdomyolysis
- Acute onset or exacerbation of Myalgia
- Myoglobinuria
- Chromaturia (e.g. tea-colored urine)

*Additional Investigations:*

In case of any of the adverse events above, subjects need to have evaluations of myoglobinuria, CK, renal function (eg, serum cystatin C) and serum chemistry two or three times weekly until values reach usual/pre-event levels or stabilize.

In addition, investigators should obtain a more detailed history of symptoms, preceding activity and hydration status, concomitant drug use, and recent or concurrent infections. Additional evaluations, including rheumatology/immunology consultations and anti-muscle antibodies, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

### 10.3.5. Clinical Safety Laboratory Evaluations

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

| | |
|---|---|
| Chemistry: | Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen, albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, alanine aminotransferase, aspartate aminotransferase, GGT, GLDH, C-reactive protein, creatine kinase (CK), and serum cystatin C |
| Hematology: | Complete blood count with differential |
| Coagulation Screen: | Prothrombin time, International Normalized Ratio, and activated partial thromboplastin time |

Persistent, unexplained abnormalities on routine renal blood test monitoring will result in additional renal function tests such as eGFR and 24-hour urine testing for protein.

A description of blood volumes to be drawn is provided in Section 17.1.

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will determine whether abnormal assessment

results are clinically significant or not. Clinical significance is defined as any variation in assessment results that has medical relevance resulting in an alteration in medical care. If clinically significant deterioration from Baseline levels is noted, the Investigator will continue to monitor the patient with additional assessments until:

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

#### 10.3.5.1. Laboratory Assessments of Interest

The review of the DMC will include evaluation of laboratory assessments of interest, which include:

- Any moderate or serious event without an alternative etiology that the Investigator deems is related to study drug
- Two consecutive, study drug-related serum creatinine levels ≥ 2 × ULN, without an alternative etiology.
- CK levels >50,000 U/L
- A confirmed, unexplained increase in GGT or GLDH > 3 × ULN and either an increase in bilirubin > 2 × ULN or nascent prothrombin time > 2 × ULN, concurrently, without an alternative etiology

### 10.3.6. Electrocardiogram

Twelve-lead ECGs will be obtained at the time points specified in Table 2. ECGs will be performed at a consistent time of day throughout the study, but before performing any invasive procedures (ie, blood sampling or study drug infusions). ECGs should be performed by trained staff after the patient is in the supine position, resting, and quiet, when possible. ECG findings will be manually reviewed and interpreted by medically qualified personnel, using a central vendor, according to prespecified criteria. The Investigator will review the results of the centrally-read ECG report and determine if the findings are clinically significant.

Clinical significance is defined as any variation in ECG findings that has medical relevance resulting in an alteration in medical care. If clinically significant worsening from Baseline is noted, the Investigator will continue to monitor the patient with additional assessments until:

- Findings have returned to normal and/or Baseline levels, or
- In the judgment of the Investigator together with the Sponsor Medical Monitor, abnormal findings are assessed to be not related to the administration of IP or other protocol-specific procedures, and additional assessments are not medically indicated.

### 10.3.7. Concomitant Medications and Therapies

Concomitant medications, changes in the dosage of concomitant medications, and concomitant therapies will be reviewed and recorded at each visit from the time the patient and/or parent/legal guardian provides signed informed consent. Information on any physiotherapeutic interventions

must be collected in detail for this study. See Section 9.4 for details on permitted concomitant medications.

#### 10.3.8. Adverse Events

AEs will be monitored throughout the study, from signing of the informed consent form through each patient's Safety Follow-up visit, which will occur approximately 4 weeks after the last eteplirsen infusion, regardless of the patient's duration in the study.

## 10.4. Pharmacokinetic Assessments

Not applicable.

## 10.5. Exploratory Assessment

#### 10.5.1. CCI Scale

The CCI is to be performed by qualified, trained staff.

The CCI is a clinician-administered scale that rates patient performance on various functional activities (Mazzone 2011). It was designed to be used in boys with DMD who are able to stand, and has been used in young boys with DMD (Connolly 2013, Mercuri 2016). During this assessment, patients perform 17 different functional activities, including a 10-meter walk/run, rising from a sit to stand, standing on one leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping.

Patients will be graded as follows: 2 = normal, no obvious modification of activity; 1 = modified method but achieves goal independent of physical assistance from another; and 0 = unable to achieve goal independently. Patients will only undergo testing of additional items that have not already been assessed before (eg, "standing on heels"), to allow for calculation of the CCI.

Details on administration of the additional CCI test items are provided in the Clinical Evaluator Manual.

# 11. ADVERSE EVENTS

## 11.1. Collection of Adverse Events

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

All AEs from the time of signed informed consent through the Safety Follow-up visit (which will occur approximately 4 weeks after the last infusion of eteplirsen, regardless of the patient's duration in the study) will be recorded in each individual patient's electronic case report form (eCRF). If at any time after the patient has completed participation in the study, the Investigator or study staff becomes aware of a SAE that the Investigator believes is related to the IP (Section 11.3.1) or is related to a study procedure (Section 11.3.2), then the event and any known details must be reported promptly to the Sponsor.

## 11.2. Definition of Adverse Events

### 11.2.1. Adverse Event

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

Adverse events include:

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

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

An AE will be defined as a treatment-emergent adverse event (TEAE) if it developed or worsened in the period from the first dose of study drug to 28 days after the last dose of study drug.

### 11.2.2. Serious Adverse Event

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

- **Death**: The patient died as the result of the event.
- **Life-threatening event**: Any AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred ie, does not include an AE that had it occurred in a more severe form, might have caused death.
- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be

part of the study, only hospitalizations that are longer than expected, based on Investigator judgment, will be considered prolonged hospitalizations.

- **Persistent or significant disability/incapacity**: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the IP.
- **Important medical event**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

## 11.3. Classification of Adverse Events

Each AE, whether serious or nonserious, will be classified by the Investigator according to the following rules and definitions.

### 11.3.1. Relationship to Investigational Product

For each AE, the Investigator will determine whether there is a reasonable likelihood that the AE may have been caused by the study treatment, according to the categories below:

| | |
|---|---|
| **Unrelated:** | There is no reasonable possibility that the event is related to the investigational drug product. |
| **Related:** | There is a reasonable possibility that the event is related to the investigational drug product. |

Adverse events that the Investigator or Sponsor considers to be related to the IP will be considered adverse drug reactions.

A treatment-related TEAE will be defined as a TEAE that the Investigator considers related to the study treatment.

### 11.3.2. Relationship to Study Procedures

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

| | |
|---|---|
| **Unrelated:** | There is no reasonable possibility that the event is related to the study procedures. |
| **Related:** | There is a reasonable possibility that the event is related to the study procedures. |

### 11.3.3. Relationship to Underlying Disease

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

| | |
|---|---|
| **Unrelated:** | There is no reasonable possibility that the event is related to the underlying disease. |
| **Related:** | There is a reasonable possibility that the event is related to the underlying disease. |

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

### 11.3.4. Severity of Adverse Events

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

The Investigator will assess the severity of all AEs as mild, moderate, or severe, based on the following definitions:

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

### 11.3.5. Outcome

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

### 11.3.6. Action Taken Regarding the Investigational Drug Product

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

### 11.3.7. Expectedness of an Adverse Event

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

### 11.3.8. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) will be handled by appropriate personnel at the Sponsor or designee, and reported within the required timelines in an unblinded fashion to regulatory authorities and the IRBs/IECs, per the requirements of the concerned competent bodies. All SUSARs will also be reported to study Investigators.

### 11.3.9. Adverse Events of Special Interest

Adverse events of special interest are AEs (serious or nonserious) that are of special scientific and/or medical interest, for which ongoing and rapid communication by the Investigator to the sponsor is appropriate.

The AESIs for this study are listed below. All AESIs should be reported as AEs to the sponsor within 24 hours of awareness irrespective of adverse event seriousness. This includes the events below that are based on lab abnormalities, which should be translated to an appropriate adverse event term at the time of reporting.

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

**Thrombocytopenia**

- Platelet count < 75,000/$mm^3$

**Infusion-related reactions**

- All infusion related reactions considered severe (see Section 11.3.4), occurring within 24 hours of the eteplirsen infusion, should be reported to the Sponsor within 24 hours of awareness.

Infusion-related reactions may include headache, vomiting, diarrhoea, pyrexia, abdominal pain, upper, flushing and nausea. There may be pain at the site of the infusion as well as bruising surrounding the infusion site. Infections are also possible at the site of the infusion.

**Rhabdomyolysis**

- Rhabdomyolysis adverse events regardless of severity

## 11.4. Recording Adverse Events

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

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

## 11.5. Reporting Adverse Events

It is the responsibility of the Investigator that reporting is done adequately. To meet regulatory reporting timelines, the study site is obligated to report any SAE(s) to the Sponsor or designee immediately and no later than 24 hours after receiving information of an event that meets at least one of the criteria for seriousness as defined in Section 11.2.2.

## 11.6. Death

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

## 11.7. Special Situations

### 11.7.1. Overdose

An overdose is defined as administration of a dose that is > 10% higher than the assigned dose per the protocol. An overdose is not an AE. An overdose will be reported even if it does not result in an AE. An overdose will be recorded on the appropriate form and sent to the Sponsor or designee within 24 hours.

### 11.7.2. Medication Error

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm, while the study drug is in the control of the health care

professional, or in certain cases, the patient. Such incidents may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, dispensing, nomenclature, compounding, distribution, administration, education, monitoring, and use.

### 11.7.3. Accidental/Occupational Exposure

An accidental/occupational exposure is the unintentional exposure to a study treatment as a result of one's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (eg, study drug given to wrong patient).

### 11.7.4. Pregnancy

If the female partner of a treated male subject becomes pregnant, the male subject must notify the Investigator within 24 hours of learning of the pregnancy. The Investigator must make every effort to ensure that the pregnant female is aware of the need to notify her healthcare provider regarding her male partner's participation in this clinical trial and his potential exposure to IP. The study site must complete a pregnancy form and send to the Sponsor or designee within 24 hours of learning of the pregnancy. The study site will make every effort to follow the pregnancy until outcome is known.

### 11.7.5. Reporting Special Situations

All occurrences of overdose, medication error, and accidental or occupational exposure with study treatment (regardless of whether an AE or SAE has occurred) must be reported on the designated special situations form as soon as possible. If the overdose, medication error, or accidental or occupational exposure is associated with an SAE, the SAE must be reported on an SAE Report Form within 24 hours.

### 11.7.6. Responsibilities of the Investigator

The responsibilities of the Investigator include, but are not limited to, the following:

- Monitoring and recording all AEs
- Determining seriousness, severity, and relationship to IP and/or study procedures and/or underlying disease
- Determining the onset and end date of each event
- Providing initial report of all SAEs within 24 hours of knowledge to the Sponsor or designee
- Providing follow-up information on SAEs in a timely and proactive manner
- Responding to queries regarding AEs and SAEs in a timely manner
- Ensuring that source documentation for all AEs is accurate and complete
- Ensuring that the study is conducted as defined in this protocol

### 11.7.7. Responsibilities of the Sponsor

The responsibilities of the Sponsor include, but are not limited to, the following:

- Training of Investigator and site staff on AE/SAE definitions, safety assessments, and site obligations related to safety monitoring and reporting of AE/SAEs
- Training with regard to the accurate and legal reporting of SAEs to all applicable regulatory bodies, IRBs/IECs, clinical trial sites, and other parties as appropriate and required within the regulated timing
- Safety monitoring and recording of AEs
- Adverse event processing and submission of expedited serious, unexpected, and related AEs to regulatory authorities per regulatory requirements
- Notification of expedited SAEs to sites
- Annual safety reporting to regulatory authorities and IRBs/IECs according to regional requirements

# 12. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

## 12.1. Recording of Data

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

## 12.2. Quality Assurance

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

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

The Investigator must make study files and data accessible to the study monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors.

## 12.3. Retention of Study Documents

At study completion, all eCRF data for an individual site will be copied onto a compact disc and provided to the Investigator for retention in the study files. The supporting site study files must be retained by the Investigator for a period of 3 years after the investigation is discontinued and regulatory authorities are notified.

However, these documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed upon designee.

Patient records or other source data must be kept for the maximum period mandated by the hospital, institution, or private practice, but not less than 15 years.

If offsite archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

# 13. STATISTICS

## 13.1. General Considerations

Details of the statistical methods for this study will be described in a Statistical Analysis Plan (SAP).

## 13.2. Analysis Endpoints

The study endpoints are listed in Section 7.3.

## 13.3. Determination of Sample Size

There is no formal sample size calculation. As this study is an OLE study of Study 4658-102, the sample size will be predicated on the sample size of Study 4658-102.

## 13.4. Analysis Sets

There will be one analysis population, the Safety Analysis Set, which includes all patients who are enrolled in the study and receive at least 1 dose of eteplirsen. This analysis set will be used for analyses of all endpoints, unless stated otherwise.

## 13.5. Disposition, Demographics, and Baseline Characteristics

The number and percentage of patients completing the study through Week 284 (ie, "completers") or prematurely discontinuing before Week 284 will be summarized. Disposition will also be summarized over the entire 284-week duration of the study. Reasons for premature discontinuation will also be summarized.

Demographic characteristics will be summarized by age cohort and overall. Demographic data and Baseline characteristics will be presented in data listings.

## 13.6. Exposure

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

## 13.7. Safety Analysis

Safety endpoints will be summarized for the Safety Analysis Set. All safety data will be presented in the data listings.

### 13.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher.

All AEs will be classified as either TEAEs or non-TEAEs. An AE will be considered a TEAE if it occurs at or after the start of study drug administration and within 4 weeks after the last study drug administration. An AE that does not meet the TEAE definition will be classified as a non-TEAE.

Treatment-emergent AEs will be summarized using the number and percentage of patients reporting AEs, by MedDRA system organ class (SOC) and preferred term (PT), for each dose

level and for the overall study population. The ordering of AEs will be based on the AE rate in the overall study population.

In general, summaries will have AEs categorized into all TEAEs and treatment-related TEAEs. Treatment-related TEAEs will be defined as those that the Investigator considers to be related to the study treatment (Section 11.3.1).

The following summary tables will be produced:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- SAEs
- AESIs
- AEs leading to study treatment discontinuation
- AEs leading to study withdrawal
- Deaths

The following listings will be produced:

- All TEAEs
- Non-TEAEs
- SAEs
- AESIs
- AEs leading to study treatment discontinuation
- AEs leading to study withdrawal
- Deaths and reasons for deaths

### 13.7.2. Other Safety Endpoints

Clinical laboratory assessments (chemistry, hematology, renal function, coagulation, and urinalysis), vital signs, ECG findings, physical examination findings, and weight and height will be summarized descriptively.

### 13.7.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded by PT using the most recent World Health Organization Drug Dictionary (WHODrug) version (December 2017 or later). The number and percentage of patients in the Safety Analysis Set with concomitant medications will be tabulated by Anatomical Therapeutic Chemical classification pharmacological subgroup and WHODrug PT by dose level.

At each level of summarization, a patient will be counted once if 1 or more medications at that level have been reported for that patient.

## 13.8. Exploratory Analysis

Change from Baseline to Week 144, Week 192, and Week 284 in CCI score is the exploratory variable for this study.

Exploratory analyses of scores from the CCI assessments will be performed using descriptive statistics for actual values and changes from Baseline, by visit, for each age cohort and overall. Graphical representations will be produced, as appropriate.

## 13.9. Other Statistical Issues

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

# 14. SPECIAL REQUIREMENTS AND PROCEDURES

## 14.1. Compliance with Ethical and Regulatory Guidelines

This study will comply with International Council for Harmonisation - Good Clinical Practice, with the latest version of the Helsinki declaration and with applicable national regulations, as well as with the European Union Directive 2001/20/EC.

## 14.2. Institutional and Ethics Review

Before enrollment of patients into the study, the protocol and informed consent (for parents/legal guardians) documents will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol and all substantial changes to the trial documentation will be subjected to the same IRB/IEC and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the IP during the study. IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB/IEC and the regulatory authority should be retained in the study regulatory files.

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

Written informed consent from each patient and/or patient's parent(s) or legal guardian(s) must be obtained prior to any study-specific evaluation being performed. A copy of the signed informed consent documents will be given to the patient and/or patient's parent(s) or legal guardian(s); the Investigator will retain the original copies of these documents.

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

## 14.4. Compliance with the Protocol

All processes and procedures defined in this protocol will be adhered to. Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed by the Investigator as crucial for the safety and wellbeing of that patient may be instituted for that patient only and documented as deviations. The Investigator will contact the Medical Monitor as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB/IEC; however, the IRB/IEC and Medical Monitor must be notified in writing as soon as possible, in accordance with the IRB/IEC policies, after the departure has been made.

## 14.5. Confidentiality

### 14.5.1. Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, except for information that is required by law or regulations to be disclosed to the IRB/IEC, the patient's parent(s) or

legal guardian(s), or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current global data protection standards (eg, Health Insurance Portability and Accountability Act [HIPAA], General Data Protection Regulations [GDPR]).

### 14.5.2. Patient Confidentiality

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

# 15. STUDY DOCUMENTATION AND GENERAL INFORMATION

## 15.1. Essential Study Documents

Essential study documents are among the critical documents required before study enrollment is to occur. Essential documents, as well as supplemental information, such as the Investigator's Brochure, Pharmacy Manual, and eCRF Completion Guidelines, as specified in the Study Manual and/or regulatory binder, must be kept onsite in a designated study site file.

The study site files will also contain, but are not limited to, patient accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB/IEC correspondence, deviations, biological sample records, and SAE and Investigational New Drug safety reports/Safety Alert Letters.

## 15.2. General Information

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

## 15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is strictly confidential. This information may be disclosed only as deemed necessary by the Sponsor. At the conclusion of this clinical study, a clinical study report will be prepared. In addition, a manuscript may be prepared for publication in a reputable scientific journal under the direction of the Sponsor. The Sponsor will publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by the Sponsor, as detailed in the Clinical Trial Agreement. The study will be registered in the European Clinical Trials database and on ClinicalTrials.gov. After completion of the study, results will be disseminated through the clinical trial registries of the applicable countries.

## 15.4. Product Handling and Complaints Reporting

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

# 16. LIST OF REFERENCES

Aartsma-Rus A, Fokkema I, Verschuuren J, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. Hum Mutat. 2009 Mar;30(3):293-9.

Beenakker EA, Fock JM, Van Tol MJ, et al. Intermittent prednisone therapy in Duchenne muscular dystrophy: a randomized controlled trial. Archives of Neurol. 2005;62(1):128-32.

Biggar WD, Harris VA, Eliasoph L, et al. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscular Dis. 2006 Apr;16(4):249-55.

Brooke MH, Fenichel GM, Griggs RC, et al. Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. Neurol. 1989 Apr;39(4):475-81.

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

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

Connolly AM, Florence JM, Cradock MM, et al. Motor and cognitive assessment of infants and young boys with Duchenne muscular dystrophy: results from the Muscular Dystrophy Association DMD Clinical Research Network. Neuromuscul Disord. 2013;23(7):529-39.

Eagle M, Baudouin SV, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscular Dis. 2002 Dec;12(10):926-9.

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

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

Howie, SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89:46-53.

Kohler M, Clarenbach CF, Bahler C, et al. Disability and survival in Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry. 2009 Mar;80(3):320-5.

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

Mazzone E, Vasco G, Sormani MP, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology. 2011;77(3):250-6.

Mercuri E, Coratti G, Messina S, et al. Revised CCI for young boys with Duchenne muscular dystrophy. PLoS One. 2016 Aug 5;11(8):e0160195.

Pradhan S, Ghosh D, Srivastava NK, et al. Prednisolone in Duchenne muscular dystrophy with imminent loss of ambulation. J Neurol. 2006;253(10):1309-16.

PTC Therapeutics International Limited. Summary of Product Characteristics for Translarna (ataluren) in the European Public Assessment Report (last updated 14 January 2016). Available

from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002720/human_med_001742.jsp&mid=WC0b01ac058001d124

# 17. APPENDICES

## 17.1. Appendix 1: Estimated Blood Volumes to be Drawn

The World Health Organization (WHO) recommended blood volume limits should be used as a guide for blood sampling in this study (Howie 2011). Per individual, the study-related blood loss should not exceed 3% of the total volume during a 4-week period or 1% of total blood volume within a 24-hour period. Table 3 summarizes the mean blood volume per body weight for patients ≤ 10 kg and Table 4 summarizes the amount of blood required for individual sample collection.

Due to the limitations on the volume of blood collection that is considered to be acceptable in young children with very small total-circulating blood volumes, adjustments to sample collection will be made for patients weighing <10 kg. These adjustments include the use of 0.5-mL collection tubes for utilization of local laboratories for the coagulation panel.

**Table 3: Mean Blood Volume per Body Weight**

| Body Weight (kg) | Mean Total Body Blood Volume (mL) | Maximum Blood Collection Volume (mL) | |
|---|---|---|---|
| | | 24-Hour Period (1%) | 30-Day Period (3%) |
| 5.0 | 400 | 4.0 | 12.0 |
| 6.0 | 480 | 4.8 | 14.4 |
| 7.0 | 560 | 5.6 | 16.8 |
| 8.0 | 640 | 6.4 | 19.2 |
| 9.0 | 720 | 7.2 | 21.6 |
| 10.0 | 800 | 8.0 | 24.0 |

**Table 4: Blood Volume Requirements per Test**

| Test | Volume (mL) |
|---|---|
| Chemistry panel | 2.0 |
| Hematology panel | 1.0 |
| Coagulation panel[a] | 2.7 |

[a]Can be done at local laboratory in the event of blood volume limitations.