
# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **Study Title:** | A Phase 3 Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK) |
| **Study Number:** | SRP-9001-301 |
| **Version Number, Amendment Number:** | Version 5.0, Amendment 4.0 |
| **Compound Number and Name:** | Delandistrogene moxeparvovec (also known as SRP-9001) |
| **Study Phase:** | 3 |
| **Coordinating Investigator:** | PPD |
| **Sponsor Name:** | Sarepta Therapeutics, Inc. |
| **Legal Registered Address and Phone Number:** | 215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 |
| **FDA IND Number:** | 17763 |
| **EUDRACT or EU CTR Number:** | 2019-003374-91 |
| **Approval Date:** | 28-MAY-2024 |

# SIGNATURE PAGE FOR SPONSOR

| | |
|---|---|
| **Protocol Title:** | A Phase 3 Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK) |
| **Study No:** | SRP-9001-301 |

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 benefit-risk evaluation of the investigational product.
- The clinical study will be conducted in compliance with the protocol, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, Good Clinical Practice (GCP) Guidelines described in the International Council for Harmonisation (ICH) E6 (R2) and 21 Code of Federal Regulations, and applicable national regulations and directives including the European Union (EU) Clinical Practice Directive 2005/28/EC, EU No 536/2014, and Japanese GCP Regulation.

This document was e-signed; the e-signature manifest can be found on the last page.

PPD

PPD

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

Date

# INVESTIGATOR'S AGREEMENT

I have read and understood all sections of the study protocol SRP-9001-301, Version 5.0, Amendment 4.0 dated 28-MAY-2024 entitled "A Phase 3 Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK)" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol, the Good Clinical Practice (GCP) described in the International Council for Harmonization tripartite guideline E6 (R2) and in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312, applicable national regulations and directives such as the European Union (EU) Clinical Practice Directive 2005/28/EC, EU No 536/2014, Japanese GCP Regulation, and all applicable regulations, directives, and relevant parts of 21 CFR 812; relevant Sponsor policies, and conditions of approval by local requirements and regulations. I will not make changes to the protocol before consulting with Sarepta Therapeutics or implement protocol changes without Institutional Review Board/Independent Ethics Committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a delegated sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Sarepta Therapeutics.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD-MMM-YYYY)

# 2. PROTOCOL SUMMARY

## 2.1. Synopsis

<table>
<tr><td>NAME OF COMPANY:<br>Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000</td><td>NAME OF FINISHED PRODUCT:<br>delandistrogene moxeparvovec<br><br>NAME OF ACTIVE INGREDIENT:<br>delandistrogene moxeparvovec</td></tr>
<tr><td colspan="2">Title of Study: A Phase 3 Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK)</td></tr>
<tr><td colspan="2">Study Number: SRP-9001-301</td></tr>
<tr><td colspan="2">Number of Study Sites: This is a multinational clinical study, to be conducted at approximately 40 sites.</td></tr>
<tr><td colspan="2">Phase of Development: Phase 3</td></tr>
<tr><td colspan="2">Indication: Duchenne muscular dystrophy (DMD)</td></tr>
<tr><td colspan="2">Rationale : Duchenne muscular dystrophy is a rare, serious, debilitating, and ultimately fatal disease for which there is an urgent need to develop safe and effective therapies. To meet this urgency and the needs of the patient community, this study evaluates the effect of delandistrogene moxeparvovec (also known as SRP-9001) compared with placebo in subjects with DMD. Gene replacement therapy has been studied for the past 10 to 15 years and shows favorable results in nonclinical studies in species deficient in dystrophin. The goal of delandistrogene moxeparvovec therapy is to induce the expression of the delandistrogene moxeparvovec dystrophin protein in skeletal and cardiac muscle in order to increase strength and protect from contraction-induced injury. Correction of the underlying genetic defect in DMD using gene replacement with delandistrogene moxeparvovec is a promising treatment.</td></tr>
<tr><td colspan="2">Objectives and Endpoints:
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• To evaluate the effect of delandistrogene moxeparvovec on physical function as assessed by the North Star Ambulatory Assessment (NSAA) score</td><td>• Change in NSAA total score from Baseline to Week 52 (Part 1)</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To evaluate the effect of delandistrogene moxeparvovec on physical function as assessed by:<br>– Number of skills gained or improved on the NSAA</td><td>• Number of skills gained or improved at Week 52 (Part 1) as measured by the NSAA</td></tr>
</table></td></tr>
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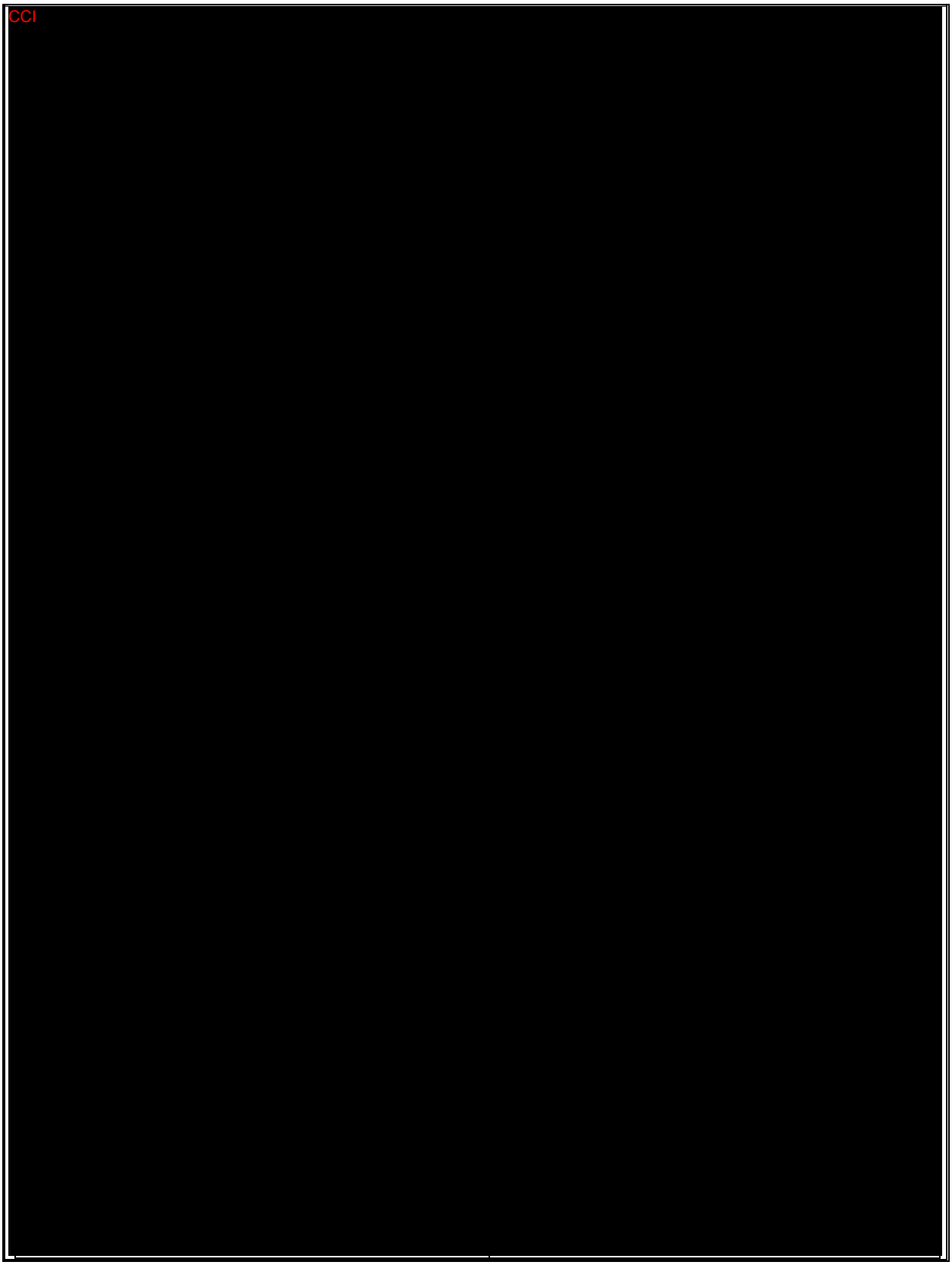
| **NAME OF COMPANY:**<br>Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | **NAME OF FINISHED PRODUCT:**<br>delandistrogene moxeparvovec<br><br>**NAME OF ACTIVE INGREDIENT:**<br>delandistrogene moxeparvovec |
|---|---|
| • To evaluate delandistrogene moxeparvovec dystrophin expression from delandistrogene moxeparvovec at 12 weeks (Part 1) as measured by western blot of biopsied muscle tissue | • Quantity of delandistrogene moxeparvovec dystrophin protein expression at Week 12 (Part 1) as measured by western blot |
| • To evaluate the effect of delandistrogene moxeparvovec on timed function tests as assessed by measuring:<br>– Time to rise from the floor<br>– 100-meter walk/run (100MWR)<br>– Time to ascend 4 steps<br>– 10-meter walk/run (10MWR) | • Change in time to rise from the floor from Baseline to Week 52 (Part 1)<br>• Change in time of 100MWR from Baseline to Week 52 (Part 1)<br>• Change in time to ascend 4 steps from Baseline to Week 52 (Part 1)<br>• Change in time of 10MWR from Baseline to Week 52 (Part 1) |
| • To evaluate the effect of delandistrogene moxeparvovec on stride velocity 95th centile (SV95C) as measured by a wearable device | • Change in SV95C from Baseline to Week 52 (Part 1) |
| • To evaluate subject (parent/caregiver proxy) reported Mobility and Upper Extremity Function using the Patient Reported Outcomes Measurement Information System (PROMIS®) tool | • Change in PROMIS score in Mobility and Upper Extremity from Baseline to Week 52 (Part 1) |
| • To evaluate the safety of delandistrogene moxeparvovec | • Incidence of treatment-emergent adverse events<br>• Incidence of serious adverse events<br>• Incidence of adverse events of special interest<br>• Clinically significant changes in vital signs and physical examination findings<br>• Clinically significant changes in safety laboratory assessments, electrocardiograms (ECGs), and echocardiograms (ECHOs) |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|---|---|
| **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>delandistrogene moxeparvovec<br><br>**NAME OF ACTIVE INGREDIENT:**<br>delandistrogene moxeparvovec |
| CCI [redacted] | |

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CCI [redacted]

**Methodology:**
This is a randomized, double-blind, placebo-controlled 2-part study of systemic gene delivery of delandistrogene moxeparvovec in approximately 120 male DMD ambulatory subjects ≥ 4 to < 8 years of age. Randomization will be stratified CCI [redacted]. All patients will have the opportunity to receive intravenous (IV) delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) in either Part 1 or Part 2. The study will consist of 4 periods as follows:

- A Screening Period (pre-infusion) which begins a maximum of 31 days prior to the Day 1 infusion and during which disease characteristics and baseline therapy will be assessed, and the pre-infusion evaluation will be completed.
- A Baseline Period (pre-infusion) which begins when eligibility is confirmed and ends on the day prior to the Day 1 infusion during which baseline assessments will be completed.
- An Infusion Period during which a single IV infusion of blinded delandistrogene moxeparvovec or placebo will be administered within 31 days of obtaining the rAAVrh74 enzyme-linked immunosorbent assay (ELISA) sample. Approximately 60 subjects will receive IV delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) and approximately 60 subjects will receive placebo (saline, 0.9% sodium chloride solution) in the Infusion Period in Part 1. In the Infusion Period in Part 2, subjects who received placebo in Part 1 will receive IV delandistrogene moxeparvovec, and subjects who received delandistrogene moxeparvovec in Part 1 will receive placebo. All subjects, parents/caregivers, Investigators, and site staff, with the exception of the unblinded site pharmacist, will be blinded to subject treatment

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(delandistrogene moxeparvovec or placebo). Refer to the study blinding plan for additional details. Starting the day prior to the infusion, all subjects will receive additional glucocorticoid (prednisone equivalent) for at least 60 days.

- A 104-week Follow-up Period (post Part 1 infusion) during which safety and efficacy parameters will be evaluated in Part 1 and Part 2. Subjects will be expected to attend both remote and in-person visits to complete required procedures/assessments. Additional unscheduled visits are allowed per the Investigator's clinical judgement. For subjects who complete the study, the last study visit will occur at Part 2 Week 52. For subjects who prematurely discontinue post-infusion follow-up, an end of study/early termination visit will be required; however, each subject should be strongly encouraged to continue study follow-up until 52 weeks post each infusion.

Efficacy assessments will include the following:

- NSAA
- Time to rise from the floor
- 100MWR
- Time to ascend 4 steps
- 10MWR
- Real-world stride velocity, CCI [redacted] as assessed by a wearable device
- Muscle biopsy in a subset of subjects
- PROMIS in a subset of subjects

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Safety assessments will include the following:

- Adverse events
- Vital signs
- Physical examination
- ECGs
- ECHOs
- Laboratory tests

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CCI [redacted]

CCI [redacted]

CCI [redacted]

After completion of the Part 2 Week 52 assessments, subjects will be eligible to enroll into an extension study to assess long-term safety and efficacy. All subjects will be followed for long-term safety and efficacy in the extension study for at least 5 years after delandistrogene moxeparvovec infusion.

**Number of Subjects (Planned):** Approximately 120 subjects will be enrolled in this study.

**MAIN INCLUSION AND EXCLUSION CRITERIA:**

**Inclusion Criteria:**

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

1. Is male at birth, ambulatory, and ≥ 4 to < 8 years of age at the time of randomization.
2. Has a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the DMD gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein.
   - Mutations between or including exons 1 to 17 are not eligible.
   - In-frame deletions, in-frame duplications, and variants of uncertain significance (VUS) are not eligible.
   - Mutations fully contained within exon 45 (inclusive) are not eligible.
3. Is able to cooperate with motor assessment testing.
4. CCI [redacted]
5. CCI [redacted]
6. Is on a stable daily dose of oral corticosteroids for at least 12 weeks before Screening and the dose and regimen are expected to remain constant (except for modifications to accommodate changes in weight) throughout the study.
7. Has rAAVrh74 antibody titers < 1:400 (ie, not elevated) as determined by an ELISA.
8. Subjects who are sexually active must agree to use, for the entire duration of the study, a condom and the female sexual partner must also use a highly effective form of birth control (eg, oral contraceptive). Refer to Appendix 1.

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9. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with the study visit schedule and all other protocol requirements.
10. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide informed consent for the subject to participate in the study.

**Exclusion Criteria**

A subject who meets any of the following criteria will be excluded from this study:

1. CCI [redacted] screening ECHO or clinical signs and/or symptoms of cardiomyopathy.
2. Has had major surgery within 3 months prior to Day 1 or planned surgery or procedures that would interfere with the conduct of the study for any time during this study.
3. Has presence of any other clinically significant illness, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection or malignancy or concomitant illness or requirement for chronic drug treatment that in the opinion of the Investigator creates unnecessary risks for gene transfer or a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability.
4. Has serological evidence of current, chronic, or active human immunodeficiency virus, hepatitis C, or hepatitis B infection.
5. Has a symptomatic infection (eg, upper respiratory tract infection, pneumonia, pyelonephritis, meningitis) within CCI [redacted] prior to Day 1.
6. Demonstrates cognitive delay or impairment that could confound motor development in the opinion of the Investigator.
7. Has had treatment with any of the following therapies according to the time frames specified:

   CCI [redacted]

   - Gene therapy
   - Cell-based therapy (eg, stem cell transplantation)
   - CRISPR/Cas9, or any other form of gene editing

   CCI [redacted]

   - Use of human growth factor or givinostat

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|---|---|

CCI [redacted]

- Any investigational medication
- Any treatment designed to increase dystrophin expression (eg, Translarna™, EXONDYS 51, VILTEPSO™)

8. Has received a live virus vaccine within CCI [redacted] or inactive vaccine within CCI [redacted] of the Day 1 visit or expects to receive a vaccination during the CCI [redacted] after Day 1.
9. Has abnormal laboratory values considered clinically significant including but not limited to:

CCI [redacted]

10. Has known hypersensitivity to delandistrogene moxeparvovec or any excipients of delandistrogene moxeparvovec.
11. Family does not want to disclose subject's study participation with general practitioner/primary care physician and other medical providers.
12. In the opinion of the Investigator, the subject is not likely to be compliant with the study.

**Study Drug, Dosage, and Mode of Administration:** delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) by single IV infusion

**Reference Therapy, Dosage, and Mode of Administration:** Placebo (saline, 0.9% sodium chloride solution) by single IV infusion

**Duration of Study:** The duration of each subject's participation in the study is expected to be approximately 108 weeks:

Pre-infusion period: Up to 31 days

Treatment and follow-up period: 104 weeks

**Statistical Methods:**

**Sample Size:**

The sample size of this study is based on the power for the primary efficacy endpoint, change in NSAA total score from Baseline to Week 52 (Part 1).

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CCI [redacted]

This sample size calculation CCI [redacted] is based on efficacy data from a double-blind, placebo-controlled, Phase 2 study as well as comparison against external controls in DMD.

**Efficacy Analyses:**

The primary endpoint and some secondary endpoints will be tested in a hierarchical manner using an appropriate multiple-testing approach that provides strong control of the familywise Type 1 error rate at a 2-sided 0.05 level. The details of the testing procedure will be specified in the statistical analysis plan (SAP).

For the primary endpoint of change in NSAA total score from Baseline to Week 52 (Part 1), summary statistics will be provided by treatment group for NSAA total score at Baseline, each post-Baseline visit in Part 1, and for change from Baseline to each post-Baseline visit in Part 1. CCI [redacted]

As the primary analysis, a restricted maximum likelihood-based mixed model repeated measures analysis will be used to compare the 2 treatment groups for change in NSAA total score from Baseline to Week 52 (Part 1). In this model, the response vector consists of the change from Baseline in NSAA total score at each post-Baseline visit in Part 1. The model will include the covariates of treatment group (categorical), visit (categorical), treatment group by visit interaction, age group at randomization (categorical), age group at randomization by visit interaction, Baseline NSAA total score, and Baseline NSAA total score by visit interaction. All covariates will be fixed effects in this analysis.

An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure results in a lack of convergence, the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random.

The superiority of delandistrogene moxeparvovec over placebo will be concluded if the test achieves statistical significance based on the multiplicity-adjusted testing procedure that will be specified in the SAP.

**Interim Analysis:** The primary analysis of the study will be performed after all subjects have completed Part 1 or have withdrawn early from Part 1. No interim analysis is planned prior to the completion of Part 1.

**Data Monitoring Committee:** A program-wide independent Data Monitoring Committee (DMC) will monitor safety, efficacy, data quality, and the integrity of study. The activities and composition of this committee are outlined in the DMC Charter.

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|---|---|
| **Benefit-Risk Assessment:** Nonclinical and clinical experience from ongoing studies demonstrates an acceptable benefit/risk profile based on robust demonstration of transduction and delandistrogene moxeparvovec dystrophin expression; reduced CK levels; and improvement in functional outcome measures; and a safety profile of monitorable, manageable, and reversible risks of study therapy. | |

## 2.2. Schema

**Figure 1: Study Design Schematic Part 1**

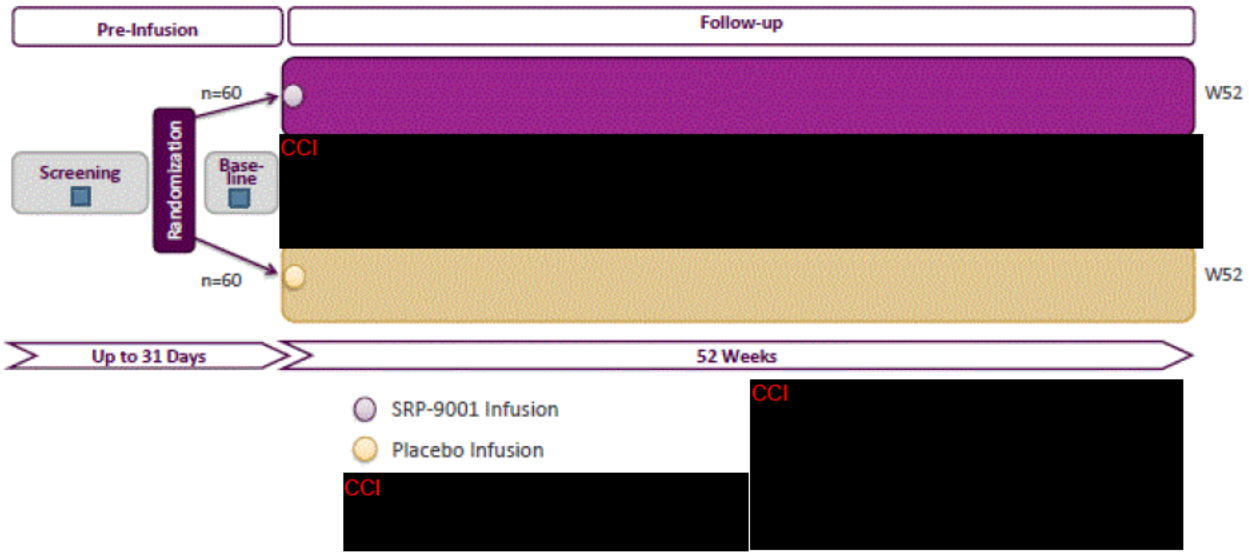
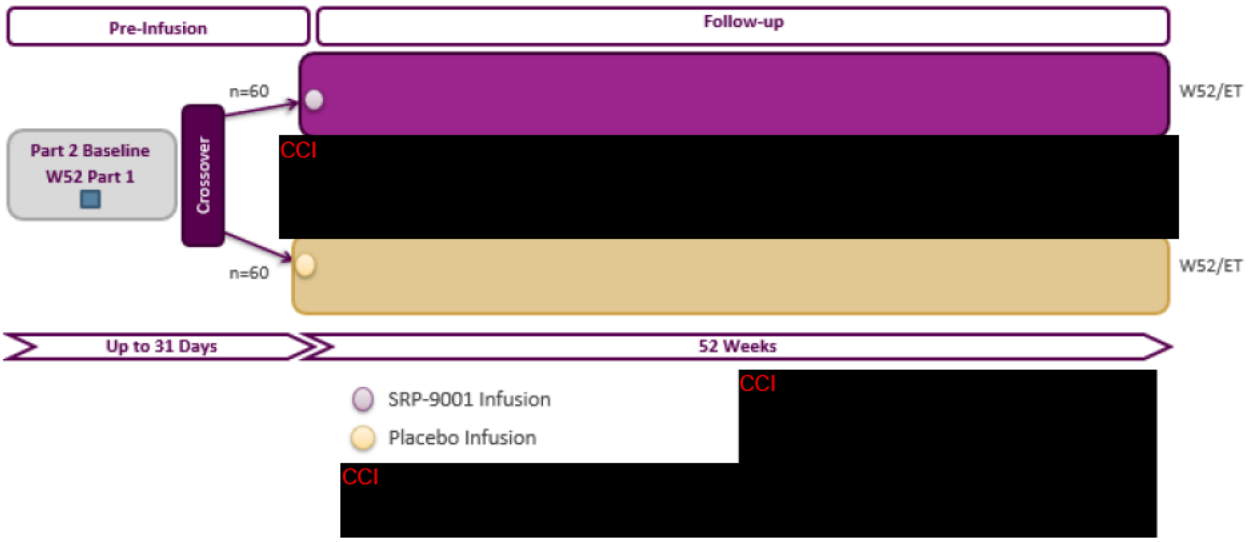
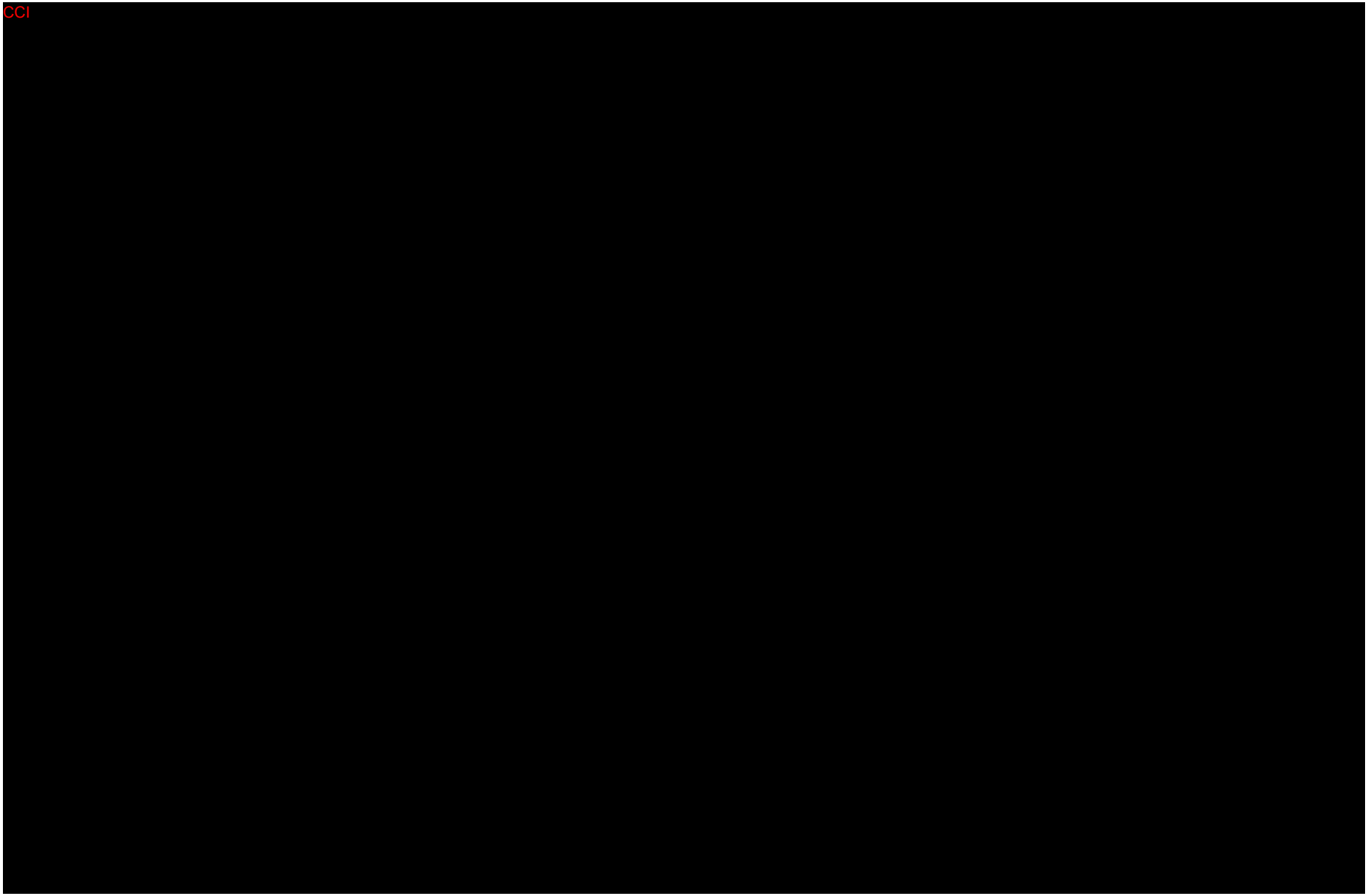



**Figure 2: Study Design Schematic Part 2 Crossover**

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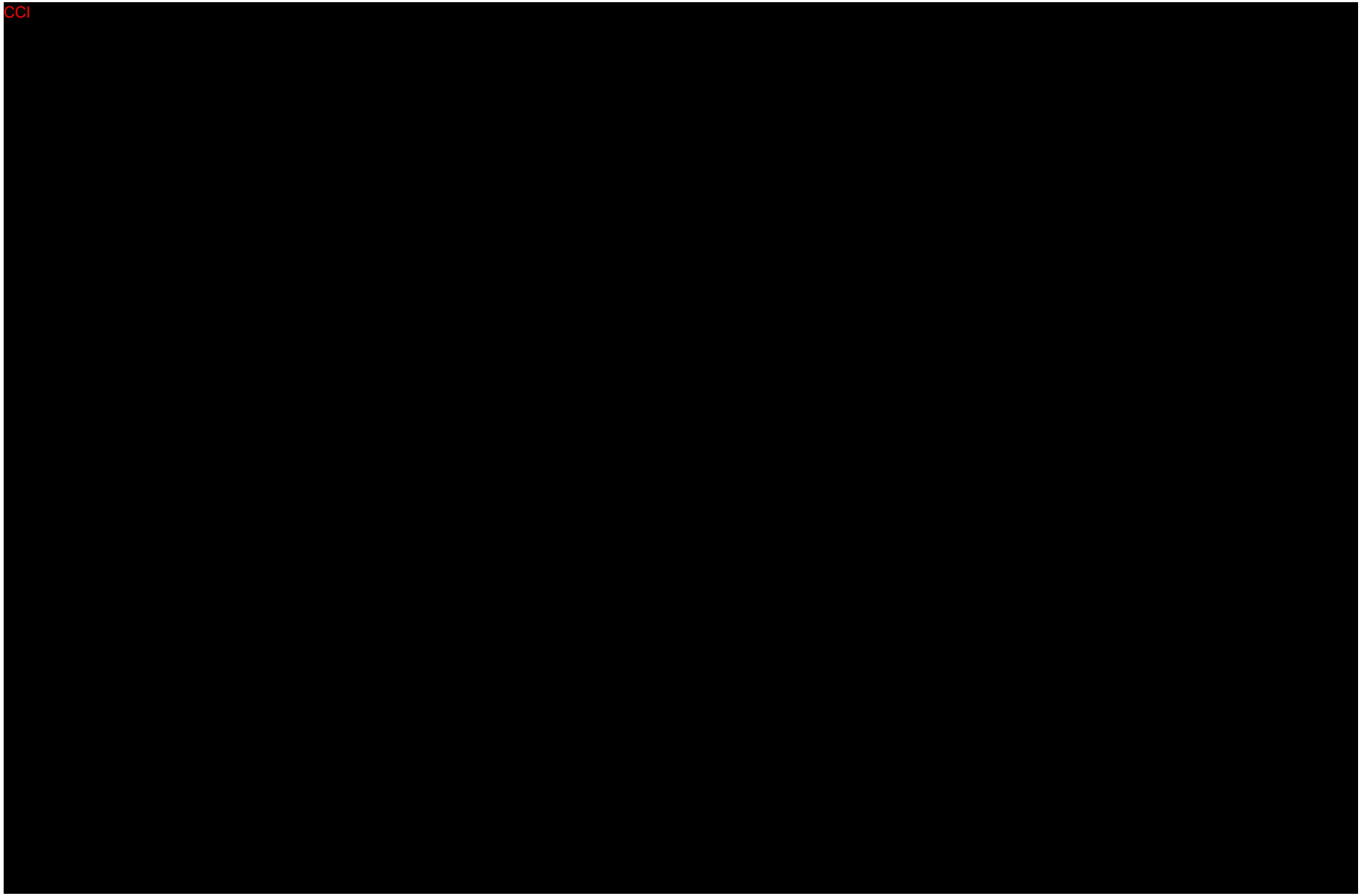
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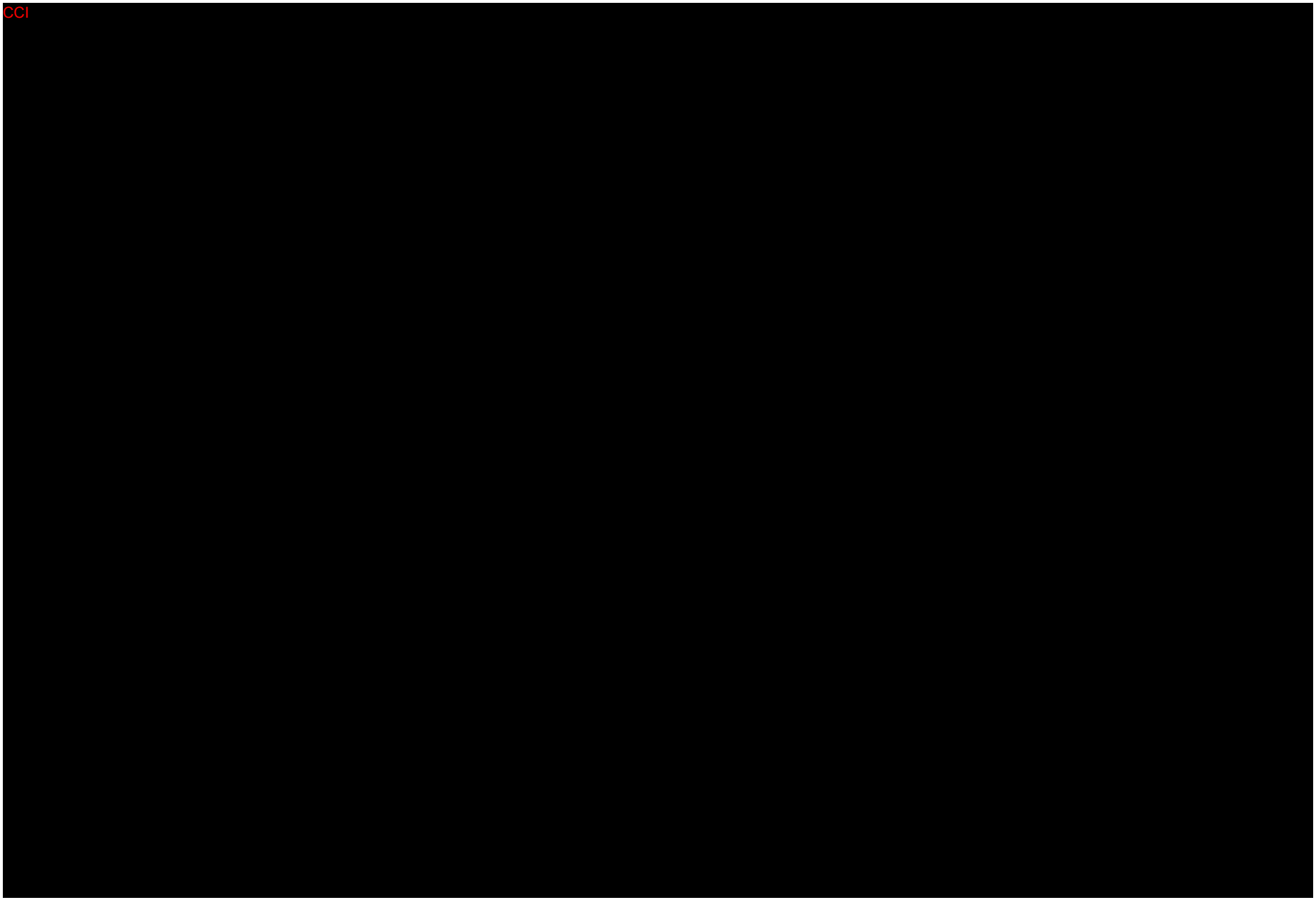
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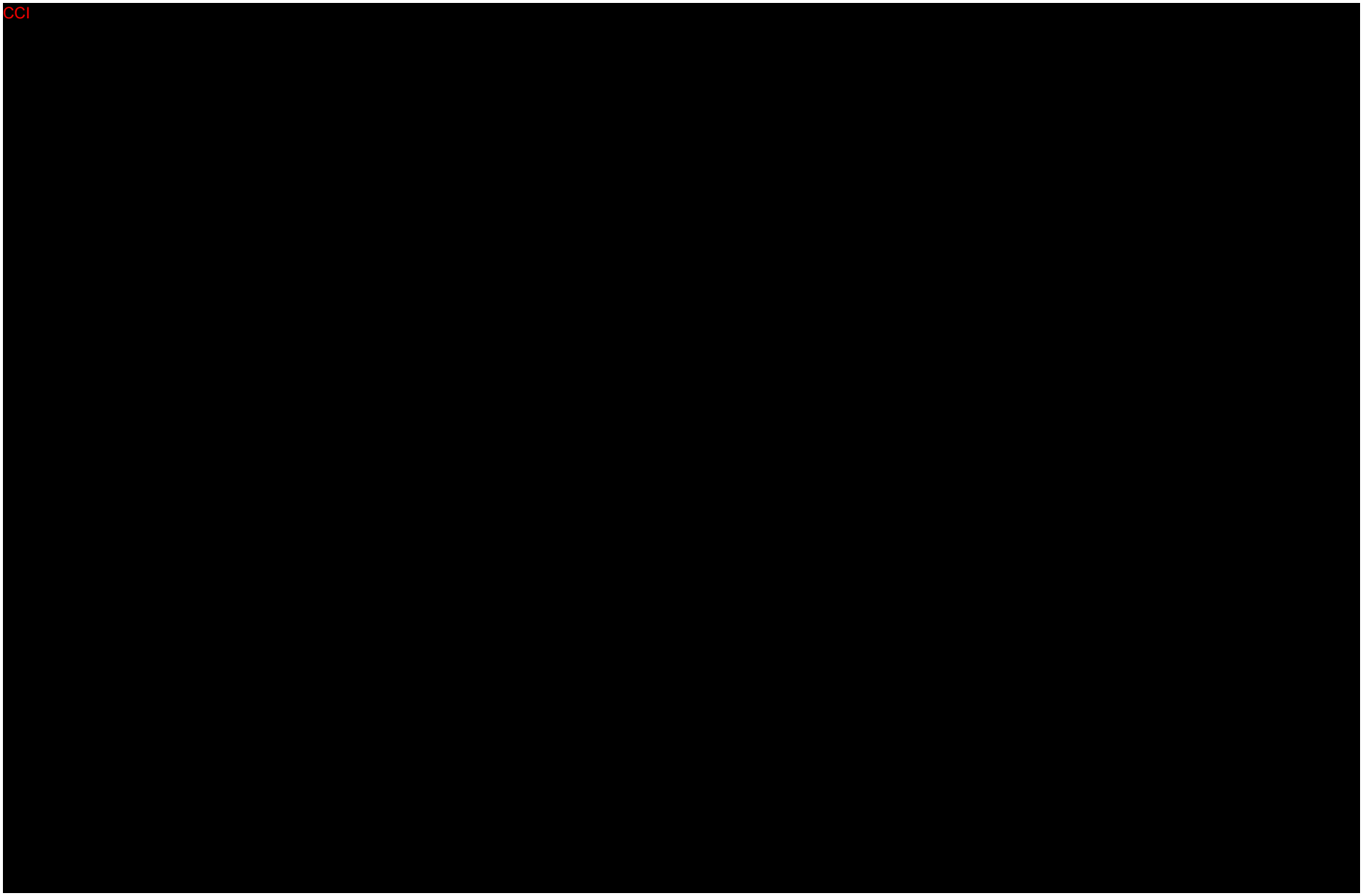
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# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

## TABLE OF CONTENTS

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## LIST OF TABLES



## LIST OF FIGURES

# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| 10MWR | 10-meter walk/run |
| 100MWR | 100-meter walk/run |
| ADL | Activities of daily living |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CFR | Code of Federal Regulations |
| CCI | CCI |
| CCI | CCI |
| CCI | CCI |
| CCI | CCI |
| CCI | CCI |
| CMV | Cytomegalovirus |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| DMD | Duchenne muscular dystrophy |
| DNA | Deoxyribonucleic acid |
| EBV | Epstein-Barr virus |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eCRF | Electronic case report form |
| ELISA | Enzyme-linked immunosorbent assay |
| CCI | CCI |
| CCI | CCI |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| GLDH | Glutamate dehydrogenase |

| Abbreviation | Definition |
|---|---|
| HEENT | Head, ears, eyes, nose, throat |
| HH6 | Human Herpesvirus 6 |
| HIV | Human immunodeficiency virus |
| hsCRP | High-sensitivity C-reactive protein |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IF | Immunofluorescence |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IRT | Interactive response technology |
| ITT | Intent-to-treat |
| IV | Intravenous(ly) |
| CCI | CCI |
| mITT | Modified Intent-to-Treat |
| NSAA | North Star Ambulatory Assessment |
| PDPF | Percent dystrophin positive fibers |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | Preferred term |
| qPCR | Quantitative polymerase chain reaction |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SOC | System organ class |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| SV95C | Stride velocity 95$^{th}$ centile |
| TEAE | Treatment-emergent adverse event |
| TMA | Thrombotic microangiopathy |
| ULN | Upper limit of normal |
| VAS | Visual analog scale |
| WHODrug | World Health Organization Drug Dictionary |

# 5. INTRODUCTION

## 5.1. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked degenerative neuromuscular disease caused by mutations in the dystrophin gene. Duchenne muscular dystrophy occurs in approximately 1 in 5000 males worldwide (Mendell 2012). The mutations that cause DMD typically disrupt the dystrophin messenger ribonucleic acid reading frame and prevent production of the corresponding protein. Dystrophin is a critically important part of the protein complex that connects the cytoskeleton of a muscle fiber to the cell membrane and extracellular matrix and acts to prevent muscle membrane damage during eccentric contraction. In the absence of dystrophin, the stress of muscle eccentric contraction causes widespread chronic and progressive muscle damage and ultimately replacement by fat and fibrotic tissue. The clinical effect of this disrupted dystrophin reading frame is thus ultimately fatal.

Duchenne muscular dystrophy is usually diagnosed between the ages of 3 to 5 years (Ciafaloni 2009), when toddlers develop a waddling gait, lordosis, toe walking, calf hypertrophy, and difficulty climbing stairs. Over time, ambulation becomes increasingly abnormal. By 8 years of age, without glucocorticoids, most patients lose the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking, leading to the increased use of mobility devices such as strollers and scooters. Patients with DMD spend less time walking than healthy boys and walk more slowly than healthy boys and are significantly less active than healthy boys of similar age (McDonald 2002, McDonald 2005). By 10 to 14 years of age, most boys lose ambulation and are wheelchair dependent.

In addition to progressive muscle weakness and wasting, manifestations of DMD typically include cardiac and pulmonary symptoms in addition to several well-understood laboratory abnormalities such as an increase in serum creatine kinase (CK). While pulmonary and cardiac functions are generally normal during early childhood, they progressively worsen over time, and patients typically die from cardiac or respiratory failure in their 20s (Brooke 1983, Eagle 2002).

Boys with DMD have a resting heart rate that is consistently higher than healthy boys even when cardiac function remains normal. Although elevation in resting heart rate in this patient population is likely multifactorial, it is associated with increased risk of cardiomyopathy (Thomas 2012), which usually manifests after 10 years of age as dilated cardiomyopathy with reduced left ventricular ejection fraction. The prevalence of cardiomyopathy in DMD patients increases with age and disease progression, with the majority of patients affected by age 18 (Gulati 2005, Spurney 2014).

Subclinical impairment of respiratory muscle function occurs in ambulatory patients (Khirani 2014, Mayer 2015), but clinical impairment of respiratory function usually only happens after loss of ambulation. Respiratory insufficiency typically starts at night, resulting in disturbed sleep, morning drowsiness and headaches, loss of appetite, and frequent pulmonary infections. Congestive heart failure or sudden death occurs in 20% of patients (Mercuri 2013).

In addition to the clinical manifestations, patients with DMD have grossly elevated CK values due to leakage of the enzyme from degenerating muscle fibers (Zatz 1991). Early in the disease, CK levels are usually 50 to 300 × the upper limit of normal (ULN), and levels tend to decrease over time as muscle is lost and replaced by fibrotic tissue and fat. High transaminase levels

(alanine aminotransferase [ALT] and aspartate aminotransferase [AST] up to approximately 22 × ULN) and lactate dehydrogenase levels, originating from degenerating muscle, are also generally observed in these patients (McMillan 2011).

## 5.2. Current Treatment for Duchenne Muscular Dystrophy

To date, there are limited treatment options for patients suffering from DMD, none of which reverse the course of this debilitating and ultimately fatal disease.

Management of DMD requires a multidisciplinary approach that includes both preventive and therapeutic measures, as recommended by DMD Care Considerations Working Group and the American Academy of Neurology (Bushby 2010, AAN 2016, Birnkrant 2018, Passamano 2012). Treatment includes corticosteroids, rehabilitation and pain management, orthopedic surgery, and respiratory interventions. Treatments designed to increase dystrophin production via exon-skipping or ribosomal readthrough of premature stop codons are available in some countries for a minority of patients with mutations amenable to their mechanism of action. While these options may improve life expectancy of DMD patients, none are capable of halting or reversing the effects of the disease, only reducing the rate of decline in muscle strength, or managing the symptoms and complications associated with DMD.

At this time, there exist limited disease management-focused treatment options for DMD. A significant unmet medical need still exists for DMD patients. As a gene therapy product, delandistrogene moxeparvovec has the potential to deliver functional dystrophin, thus addressing the root cause of the disease and potentially reversing the clinical course of decline and thereby satisfying a significant unmet medical need.

## 5.3. Delandistrogene Moxeparvovec

Sarepta and F. Hoffmann-La Roche are collaborating with respect to global development of delandistrogene moxeparvovec for the treatment of patients with DMD. Delandistrogene moxeparvovec is a gene therapy designed to treat the underlying biological cause of DMD by replacing dysfunctional or missing dystrophin protein with a functional truncated dystrophin, called delandistrogene moxeparvovec dystrophin, in cardiac and skeletal muscle; the key tissues affected in this lethal degenerative disease. Thus, delandistrogene moxeparvovec may address the root cause of DMD, alter the course of the disease, and address a significant unmet medical need.

For more background information on delandistrogene moxeparvovec, refer to the Investigator's Brochure.

### 5.3.1. Nonclinical and Clinical Experience With Delandistrogene Moxeparvovec

The effects of delandistrogene moxeparvovec treatment were evaluated at 3 doses in the *mdx* mouse. Results from these studies are summarized in Section 7.3 as well as the Investigator's Brochure.

There are multiple ongoing clinical studies with delandistrogene moxeparvovec; for a detailed summary of clinical findings to date, refer to the Investigator's Brochure.

On 22 June 2023, delandistrogene moxeparvovec (ELEVIDYS) received an accelerated approval from the FDA for the treatment of ambulatory pediatric patients aged 4 through 5 years with

DMD, who have a confirmed mutation in the DMD gene. At the time of this amendment, ELEVIDYS has also been approved for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD in United Arab Emirates, Qatar, Bahrain, Kuwait, and Oman.

## 5.4. Overall Study Rationale

Duchenne muscular dystrophy is a rare, serious, debilitating, and ultimately fatal disease for which there is an urgent need to develop safe and effective therapies. To meet this urgency and the needs of the patient community, this study evaluates the effect of delandistrogene moxeparvovec compared with placebo in subjects with DMD. The endpoints selected for the study (see Section 6) are recognized as appropriate measures of disease severity and treatment effect and are widely used in clinical practice.

All subjects enrolled in this study will be on background corticosteroids allowing for assessment of the effect of delandistrogene moxeparvovec over and above improvements that would be expected from corticosteroids alone, which are the current pharmacological standard of care for most patients in real-world practice.

Gene replacement therapy has been studied for the past 10 to 15 years and shows favorable results in nonclinical studies in mice and canine species deficient in dystrophin. The goal of delandistrogene moxeparvovec therapy is to induce the expression of the delandistrogene moxeparvovec dystrophin protein in skeletal and cardiac muscle in order to increase strength and protect from contraction-induced injury. Correction of the underlying genetic defect in DMD using gene replacement with delandistrogene moxeparvovec is a promising treatment. Duchenne muscular dystrophy affects all skeletal muscles in the body, in addition to the diaphragm and heart. As such, a systemic approach is necessary to provide the best possible benefit to patients. Utilizing the rAAVrh74 serotype allows for efficient transduction of cardiac, skeletal, and diaphragm muscle without the risk of regional delivery strategies. Increased dystrophin expression in vivo may potentially improve patient's muscle function and, importantly, may preserve diaphragm and cardiac muscle. Delandistrogene moxeparvovec appears to have a favorable safety profile and to be generally well tolerated in clinical and nonclinical studies.

All subjects will be screened for pre-existing antibodies to rAAVrh74.

Subjects with mutations between or including exons 1 to 17 will be excluded from this study to minimize the risk of immune response to the expressed delandistrogene moxeparvovec dystrophin (Mendell 2010). Additional information may be found in the Investigator's Brochure.

Subjects who have exon 45 (inclusive), or in-frame deletions, in-frame duplications, and variants of uncertain significance ("VUS") on molecular characterization of the *DMD* gene will be excluded from this study. Literature suggests that patients with these mutations exhibit a milder phenotype and thus may impact efficacy results if included.


## 5.5. Benefit/Risk Assessment

Nonclinical data suggest a positive benefit/risk relationship and support the clinical investigation of delandistrogene moxeparvovec gene transduction in DMD subjects. Efficacy studies in the *mdx* mouse model of DMD have demonstrated significant functional improvements in several disease-associated phenotypes, including specific force in the tibialis anterior and diaphragm, muscle and histological improvements including central nucleation, normalization of fiber size, and decreased fibrosis. Additional information can be found in the Investigator's Brochure.

Clinical experience from ongoing Phase 1 and 2 studies demonstrates an acceptable benefit/risk profile based on robust demonstration of transduction and delandistrogene moxeparvovec dystrophin expression; reduced CK levels; and improvement in functional outcome measures ; and a safety profile of monitorable, manageable, and reversible risks of study therapy, including liver injury, nausea and vomiting, thrombocytopenia, infusion site reaction, and hypersensitivity. A risk of immune-mediated myositis in the setting of transgene immune reaction was identified in association with DMD gene mutations that are excluded from this study. Detailed information about the results of completed and ongoing clinical studies, the known and anticipated benefits and risks and expected adverse events of delandistrogene moxeparvovec may be found in the Investigator's Brochure.

# 6. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the effect of delandistrogene moxeparvovec on physical function as assessed by the North Star Ambulatory Assessment (NSAA) score | • Change in NSAA total score from Baseline to Week 52 (Part 1) |
| **Secondary** | |
| • To evaluate the effect of delandistrogene moxeparvovec on physical function as assessed by:<br>– Number of skills gained or improved on the NSAA | • Number of skills gained or improved at Week 52 (Part 1) as measured by the NSAA |
| • To evaluate delandistrogene moxeparvovec dystrophin expression from delandistrogene moxeparvovec at 12 weeks (Part 1) as measured by western blot of biopsied muscle tissue | • Quantity of delandistrogene moxeparvovec dystrophin protein expression at Week 12 (Part 1) as measured by western blot |
| • To evaluate the effect of delandistrogene moxeparvovec on timed function tests as assessed by measuring:<br>– Time to rise from the floor<br>– 100-meter walk/run (100MWR)<br>– Time to ascend 4 steps<br>– 10-meter walk/run (10MWR) | • Change in time to rise from the floor from Baseline to Week 52 (Part 1)<br>• Change in time of 100MWR from Baseline to Week 52 (Part 1)<br>• Change in time to ascend 4 steps from Baseline to Week 52 (Part 1)<br>• Change in time of 10MWR from Baseline to Week 52 (Part 1) |
| • To evaluate the effect of delandistrogene moxeparvovec on stride velocity 95th centile (SV95C) as measured by a wearable device | • Change in SV95C from Baseline to Week 52 (Part 1) |
| • To evaluate subject (parent/caregiver proxy) reported Mobility and Upper Extremity Function using the Patient Reported Outcomes Measurement Information System (PROMIS®) tool | • Change in PROMIS score in Mobility and Upper Extremity from Baseline to Week 52 (Part 1) |

| | |
|---|---|
| • To evaluate the safety of delandistrogene moxeparvovec | • Incidence of treatment-emergent adverse events (TEAEs)<br>• Incidence of serious adverse events (SAEs)<br>• Incidence of adverse events of special interest (AESIs)<br>• Clinically significant changes in vital signs and physical examination findings<br>• Clinically significant changes in safety laboratory assessments, electrocardiograms (ECGs), and echocardiograms (ECHOs) |

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# 7. INVESTIGATIONAL PLAN

## 7.1. Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled 2-part study of systemic gene delivery of delandistrogene moxeparvovec in approximately 120 male DMD ambulatory subjects who are ≥ 4 to < 8 years of age. The total duration of each subject's participation in the study is expected to be approximately 108 weeks, inclusive of an up to 4-week Pre-infusion Period (Section 7.1.1) and a 52-week treatment and follow-up period (Section 7.1.2) in Part 1 and Part 2. All subjects will have the opportunity to receive intravenous (IV) delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) in either Part 1 or Part 2.

Schematics of the study design is provided in Section 2.2. The schedules of events are provided in Section 2.3.

### 7.1.1. Pre-infusion Period

Prior to undergoing any study procedures, subjects will provide informed consent/assent and parent(s), or legal guardian(s) will provide informed consent for the subject to participate in the study.

#### 7.1.1.1. Subject Identification Number

Every subject will be assigned a CCI digit identification number CCI [redacted]. The interactive response technology (IRT) will assign subject numbers. Subject numbers will not be re-used if a subject is a screen failure. Refer to the IRT Manual for additional information.

#### 7.1.1.2. Screening Period

During the Screening Period, which begins a maximum of 31 days prior to the Day 1 infusion, various assessments will be performed.

A blood draw for an enzyme-linked immunosorbent assay (ELISA) and provision of the wearable device are required to be performed at the initial Screening visit. Subjects will be provided with a wearable device to collect daily physical activities. Subjects should attempt to wear this device CCI [redacted]. Subjects must return the wearable device in the event of screen failure, early termination, or after study completion. Refer to the Wearable Investigator Manual for additional information. It is recommended that the following assessments occur at minimum during the initial Screening visit: collection of the subject's medical history, demographics, documentation of DMD genotyping, select clinical laboratory assessments which inform eligibility, serology tests, vital signs, ECHO, the NSAA (including the timed function tests of time to rise from the floor and the 10MWR), provision of the wearable device, and full physical examination (including weight).

During the Screening Period, additional assessments will include ECG, urinalysis, and a review of adverse events (AEs) and concomitant medications and procedures. CCI [redacted]

All laboratory samples obtained will be stored CCI if permitted by the informed consent/assent form regardless of screening outcome and maintained for up to CCI following the end of the study or per local regulations.

Refer to the Schedule of Events in Section 2.3 for an outline of assessments performed during the Screening Period.

#### 7.1.1.3. Baseline Period

The Baseline Period will start when eligibility is confirmed and ends on the day prior to the Day 1 infusion. During this period, vital signs, select clinical laboratory assessments, CCI [redacted]. A brief physical examination (including height, ulnar length, and weight) will be performed. CCI [redacted]

Physical functional assessments to be performed will include the NSAA (including the timed function tests of time to rise from the floor and the 10MWR although the timed components are not part of the NSAA), time to ascend 4 steps, and the 100MWR. The NSAA will be CCI [redacted]. Functional assessment data collected at Baseline will be used for the efficacy endpoint analysis as described in Section 12.4.4 and detailed in the statistical analysis plan (SAP).

A subset of subject and parent/caregiver proxies will complete PROMIS measures CCI [redacted].

CCI [redacted]

Refer to the Schedule of Events in Section 2.3 for an outline of assessments performed during the Baseline Period.

### 7.1.2. Infusion Period

On the day prior to study drug infusion, subjects will be started on additional steroid for immunosuppression; see Section 9.5.1.1.

The study drug infusion will occur on Day 1 of Part 1 and Part 2. In Part 1, approximately 60 subjects will receive IV delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) and approximately 60 subjects will receive matching infusion volumes of placebo (saline, 0.9% sodium chloride solution). In Part 2, subjects who received placebo in Part 1 will receive IV delandistrogene moxeparvovec, and subjects who received delandistrogene moxeparvovec in Part 1 will receive placebo in order to maintain blinding throughout the study. Refer to the study-specific Pharmacy Manual for additional information.

All subjects, parents/caregivers, Investigators, and site staff, with the exception of the unblinded site pharmacist, will be blinded to the treatment the subject receives (delandistrogene moxeparvovec or placebo). Refer to the study blinding plan for further details.

On Day 1, vital signs, CCI [redacted]. A brief physical examination and an ECG will be performed. Weight for dosing should be obtained either prior to Day 1 or on Day 1; refer to the Pharmacy Manual for additional information.

Refer to the Schedule of Events in Section 2.3 for an outline of assessments performed on Day 1.

Prior to dosing in Part 2, the unblinded contract research organization (CRO) medical director will review the rAAVrh74 antibody titers and treatment allocation and communicate whether dosing may proceed.

### 7.1.3. 52-Week Follow-up Period

Subjects will receive 1 mg/kg additional glucocorticoid (prednisone equivalent) for at least 60 days after the infusion; however, earlier tapering to manage an AE may be permitted with Medical Monitor approval in Part 1 and Part 2. Post-infusion added glucocorticoid for immunosuppression should be increased to 2 mg/kg daily if gamma-glutamyl transferase (GGT) level is confirmed to be CCI [redacted] U/L or there are other clinically significant liver function abnormalities following infusion. A tapering dose of glucocorticoid will be implemented based on individual subject's response to the infusion as assessed by liver function monitoring with GGT. Refer to Section 9.5.1.2.

Subjects will be followed for up to 52 weeks in Part 1 and Part 2 and will complete follow-up visits at the following time points: CCI [redacted]

Safety will be assessed by monitoring of vital signs, physical examinations, ECGs, ECHOs, TEAEs, SAEs, and select laboratory assessments.

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Physical functional assessments will be performed throughout the study and will include the NSAA (including the timed function tests of time to rise from the floor and the 10MWR although the timed components are not part of the NSAA), time to ascend 4 steps, and the 100MWR.

Subjects will be provided with a wearable device to collect daily physical activities. Subjects should attempt to wear the device CCI [redacted]. Subjects must return the wearable device in the event of screen failure, early termination, or after study completion. Refer to the Wearable Investigator Manual for additional information.

A subset of subject and parent/caregiver proxies will complete PROMIS Mobility, Upper Extremity CCI [redacted] domains (proxy report for pediatric), CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

#### 7.1.3.1. End of Study/Early Termination

For subjects who complete the study, the last study visit will occur at Week 52 of Part 2. For subjects who terminate the study early, an early termination visit will be required as shown in the Schedule of Events (Section 2.3).

The NSAA (including the timed function tests of time to rise from floor and 10MWR although the timed components are not part of the NSAA), will be completed CCI [redacted].

After completion of the Part 2 Week 52 assessments, subjects will be enrolled into an extension study to assess long-term safety and efficacy. Subjects will be followed for long-term safety and efficacy in the extension study. Subjects will be followed for at least 5 years following their delandistrogene moxeparvovec infusion.

### 7.1.4. Completion of the Study

The study will be considered complete when all subjects have completed the Week 52 visit of Part 2 or otherwise discontinued from the study.

Study sites who did not enroll a subject will be closed. A study site will be considered closed when all required study documents and study supplies, including wearable devices, have been collected and a study-site closure visit has been performed.

### 7.1.5. Study Discontinuation

If the Sponsor, Investigator, Medical Monitor, Study Monitor, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or appropriate regulatory/competent authority officials discover conditions arising during the study that indicate the study should be temporarily suspended or halted or that a study center should be closed, appropriate action may be taken after consultation among the Sponsor, Investigator, and others as needed.

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

- The discovery of an unexpected, serious, or unacceptable risk to subjects 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 enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory/competent authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, IRB/IEC, or regulatory/competent authority
- Insufficient adherence or noncompliance with the clinical study protocol and global GCP regulations, directives, guidelines, and laws such as the Pharmaceutical and Medical Device Act, and the clinical study protocol, as applicable

## 7.2. Scientific Rationale for Study Design

The placebo-controlled design of the double-blind treatment period was chosen to reduce potential bias during data collection and evaluation of outcome parameters. Both the placebo and delandistrogene moxeparvovec groups will be allowed to continue standard of care steroid therapy as well as non-pharmacological interventions such as physiotherapy during the study. The 52-week double-blind follow-up duration of the study provides sufficient time to obtain safety and efficacy data post infusion. The Part 2 crossover allows for all subjects to have the opportunity to receive delandistrogene moxeparvovec. Following completion of Study SRP-9001-301, subjects may enter a separate, long-term extension study where additional safety and efficacy data will be collected. In the long-term extension study subjects will be followed for at least 5 years following their delandistrogene moxeparvovec infusion.

## 7.3. Dose Selection Rationale

The dose of delandistrogene moxeparvovec selected for use in this study is $1.33 \times 10^{14}$ vg/kg (quantitative polymerase chain reaction [qPCR] with linear standard) and was chosen based on results from nonclinical studies where the delivery of delandistrogene moxeparvovec systemically demonstrated successful gene transduction to all skeletal muscles assessed, heart, and diaphragm in the *mdx* mouse model.

In addition to the clinical evidence presented in Section 5.5, the clinical dose selection is also supported by the preliminary PK/PD modeling and simulations based on clinical data integrated across Studies SRP-9001-101 and SRP-9001-102 Part 1. CCI [redacted]

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[redacted]

## 7.4. Study Committees

A program-wide independent Data Monitoring Committee (DMC) will assist in the monitoring of safety, efficacy, data quality, and the integrity of study. See Section 12.6 for details.

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

## 8.1. Inclusion Criteria

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

1. Is male at birth, ambulatory, and ≥ 4 to < 8 years of age at the time of randomization.
2. Has a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the DMD gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein.
    a. Mutations between or including exons 1 to 17 are not eligible.
    b. In-frame deletions, in-frame duplications, and variants of uncertain significance ("VUS") are not eligible.
    c. Mutations fully contained within exon 45 (inclusive) are not eligible.
3. Is able to cooperate with motor assessment testing.
4. CCI [redacted]
5. CCI [redacted]
6. Is on a stable daily dose of oral corticosteroids for at least 12 weeks before Screening and the dose and regimen are expected to remain constant (except for modifications to accommodate changes in weight) throughout the study.
7. Has rAAVrh74 antibody titers < 1:400 (ie, not elevated) as determined by an ELISA.
8. Subjects who are sexually active must agree to use, for the entire duration of the study, a condom and the female sexual partner must also use a highly effective form of birth control (eg, oral contraceptive). Refer to Appendix 1.
9. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with the study visit schedule and all other protocol requirements.
10. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide informed consent for the subject to participate in the study.

## 8.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from this study:

1. CCI [redacted] screening ECHO or clinical signs and/or symptoms of cardiomyopathy.
2. Has had major surgery within 3 months prior to Day 1 or planned surgery or procedures that would interfere with the conduct of the study for any time during this study.
3. Has presence of any other clinically significant illness, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection or

malignancy or concomitant illness or requirement for chronic drug treatment that in the opinion of the Investigator creates unnecessary risks for gene transfer or a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability.

4. Has serological evidence of current, chronic, or active human immunodeficiency virus, hepatitis C, or hepatitis B infection.
5. Has a symptomatic infection (eg, upper respiratory tract infection, pneumonia, pyelonephritis, meningitis) within CCI prior to Day 1.
6. Demonstrates cognitive delay or impairment that could confound motor development in the opinion of the Investigator.
7. Has had treatment with any of the following therapies according to the time frames specified:

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   - Gene therapy
   - Cell based therapy (eg, stem cell transplantation)
   - CRISPR/Cas9, or any other form of gene editing

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   - Use of human growth factor or givinostat

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   - Any investigational medication
   - Any treatment designed to increase dystrophin expression (eg, Translarna™, EXONDYS 51, VILTEPSO™)
8. Has received a live virus vaccine within CCI or inactive vaccine within CCI of the Day 1 visit or expects to receive a vaccination during the CCI after Day 1.
9. Has abnormal laboratory values considered clinically significant including but not limited to:

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10. Has known hypersensitivity to delandistrogene moxeparvovec or any excipients of delandistrogene moxeparvovec.

11. Family does not want to disclose subject's study participation with general practitioner/primary care physician and other medical providers.
12. In the opinion of the Investigator, the subject is not likely to be compliant with the study protocol.

## 8.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimal set of screen failure information including demography, screen failure details, eligibility criteria, and any SAE information are required to ensure transparent reporting of screen failure subjects. CCI [redacted]

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened at the Investigator's discretion with Sponsor approval.

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

Subjects will be considered to have completed their participation in the study after they have completed the Part 2 Week 52/early termination visit or have withdrawn from the study.

## 8.5. Subject Withdrawal Criteria

Any subject can decide to withdraw from study participation at any time for any reason. A subject who withdraws prior to dosing may be replaced at the discretion of the Sponsor. In addition, the Sponsor may decide to stop the study participation of any subject as deemed necessary. The Investigator may also stop the study participation of any subject at any time. Reasons for withdrawal from the study include, but are not limited to:

- The subject or parent(s)/legal guardian(s) withdraws consent.
- Prior to randomization and dosing it is determined that the subject was erroneously included in the study (ie, was found to not have met the eligibility criteria).
- The subject is unable to comply with the requirements of the protocol.
- The subject participates in another investigational study without prior written authorization of the Sponsor.

The Investigator or study staff will document the reason(s) for withdrawal on the electronic case report form (eCRF). If withdrawn subjects received study drug, every effort should be made to request that the subject allow follow-up for safety purposes.

Subjects who withdraw from the study must return the wearable device.

Subjects who have received study drug and withdraw from the study but do not withdraw consent will be asked to continue telephone calls to collect AEs and concomitant medications and have blood collected for laboratory assessments according to Section 2.3 CCI [redacted] after infusion (if subjects withdraw within this window), and then for

safety laboratory assessments approximately [redacted] starting from the date of the last safety laboratory assessment before withdrawal. For this study, safety laboratory assessments include the following: electrolytes, troponin, liver function, hematology, high-sensitivity C-reactive protein (hsCRP) and complement, renal function, and urinalysis (see Section 10.4.6.1 for a list of analytes associated with each parameter).

## 8.6. Subject Lost To Follow-up

Every effort, as allowed by local and national law, will be made by the Investigator to contact the subject before the subject is declared lost to follow-up. These efforts may include but are not limited to the following:

- Attempt to contact the subject (or if applicable, the legal guardian who signed the informed consent on behalf of the subject) with at least 3 telephone calls to all telephone numbers for subject and other listed contacts (including in the evening and on weekends) and reschedule the missed visit as soon as possible and counsel the subject (or if applicable, the legal guardian who signed the informed consent on behalf of the subject) on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to continue in the study.
- Call the primary care physician/general practitioner, referring specialist, and/or other listed physicians for more recent locator information, date of last office visit, or to determine mortality status.
- Send email and follow-up with mailing certified letters (return receipt requested) to all known subject addresses (or local equivalent methods) and all listed contacts (eg, relatives, friends, neighbors).
- Review subject's records and medical notes for any details of a hospitalization, doctor's visit, or other procedure that may indicate the status of the subject.
- Check local, regional, and national public records to locate subject or search for mortality status in accordance with local law.

All contact attempts should be documented in the subject's medical record. Once the site has exhausted and documented these actions, the subject will be considered to have withdrawn from the study.

# 9. STUDY TREATMENT

## 9.1. Description of Study Drug

Delandistrogene moxeparvovec is supplied as a sterile, single use, frozen liquid for IV infusion. The frozen drug product must be thawed prior to the clinical administration. Refer to the study-specific Pharmacy Manual for further details.

### 9.1.1. Package and Labeling

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

### 9.1.2. Study Drug Preparation

Please refer to the study-specific Pharmacy Manual for dosage preparation instructions.

### 9.1.3. Storage

Delandistrogene moxeparvovec must be stored at ≤ -60˚C.

Study drug must be stored in an access controlled, locked room with appropriate temperature recording, controls, and monitoring.

Details for storage can be found in the study-specific Pharmacy Manual.

## 9.2. Study Treatment Administered

Subjects will be randomized in a 1:1 ratio by the IRT to one of the following treatment groups:

- Delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) by single IV infusion
- Placebo (saline, 0.9% sodium chloride solution) by single IV infusion

As required by the inclusion criterion, all subjects will be on a stable daily dose of oral corticosteroids for at least 12 weeks before the Screening visit, as detailed in Section 9.5.1. The day before the infusion (delandistrogene moxeparvovec or placebo), the subject will be started on additional steroid for immunosuppression and will continue at this level for at least 60 days after the infusion (see Section 9.5.1.1). Following these 60 days, subjects may be tapered off of the added steroid and return to their baseline dose of corticosteroids for DMD and will remain on their stable dose (except for modifications to accommodate changes in weight) through the remainder of the study (see Section 9.5.1.2).

On Day 1, delandistrogene moxeparvovec or placebo administration will be through a peripheral limb vein and performed according to the Administration Instructions (or Manual). CCI [redacted] A topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream) may be applied to the skin prior to insertion of the IV catheter for infusions per site and subject preference. Prior to infusion, the IV catheter should be checked to confirm if it is within the vein and the IV flows well (is not interstitial).

## 9.3. Randomization and Blinding

### 9.3.1. Randomization

Subjects will be randomized in a 1:1 ratio by the IRT to receive either delandistrogene moxeparvovec ($1.33 \times 10^{14}$ vg/kg) or placebo (saline, 0.9% sodium chloride solution) by single IV infusion. Subjects who received delandistrogene moxeparvovec in Part 1 of the study will receive placebo in Part 2. Subjects who received placebo in Part 1 of the study will have the opportunity to receive delandistrogene moxeparvovec in Part 2.

Randomization will be stratified CCI [redacted].

### 9.3.2. Blinding/Unblinding

#### 9.3.2.1. Blinded and Unblinded Personnel

All subjects, parents/caregivers, Investigators, and site staff with the exception of the unblinded site pharmacist will be blinded to the treatment the subject receives (delandistrogene moxeparvovec or placebo). The unblinded pharmacist (or designee) will perform drug preparation according to the randomized treatment assigned. All documentation of study drug preparation will be maintained in a secure location which prevents access or disclosure to all blinded clinical study personnel. Refer to the study blinding plan for further details.

#### 9.3.2.2. Blinding for Muscle Biopsy Assessments

Blinding for muscle biopsy assessments is outlined in the Biopsy Surgical and Laboratory Manual.

#### 9.3.2.3. Unblinding Procedures

In the event of a medical emergency wherein the knowledge of the subject's treatment assignment may influence clinical decision-making, the Investigator has the option to unblind the subject's treatment assignment using the IRT system.

The blind of the treatment may be broken only in exceptional circumstances, such as when knowledge of the study treatment is essential for management of a subject's medical condition or AE. If time permits, the Investigator should contact the unblinded CRO Medical Director before unblinding the subject. If time does not permit, the Investigator may authorize breaking of the blind and then notify the unblinded CRO Medical Director. The study drug information should be disclosed only to personnel who need the information for the medical care of the subject. If the study treatment is unblinded, the subject number, time, date, and reason for unblinding must be recorded in the study records. Study personnel who were unblinded should be identified.

The reasons for any unblinding must be noted in the source documentation. The Investigator must not disclose information about treatment assignment to anyone aside from specific individuals who need the information because of their direct involvement in subject care.

Regulatory authorities and/or the IRB/IEC may request the unblinding of data from subjects at any time.

#### 9.3.2.4. Data Access

Clinical evaluators conducting the functional assessments will not have access to treatment assignment/pharmacy data or to laboratory data (eg, ELISA, CCI [redacted] GGT, etc.) during this study. Blinded personnel will not have access to the ELISA CCI [redacted] results, except for the Part 1 screening AAVrh74 ELISA results for eligibility, as post-infusion results from these tests may be unblinding.

## 9.4. Treatment Compliance

Delandistrogene moxeparvovec or placebo will be administered once by IV infusion under the direct supervision of trained study staff.

The study staff will maintain a record of the dispensing and administration of study drug for each subject via an accountability record or equivalent document.

Accurate recording of study drug administration will be made in the appropriate section of the subject's eCRF and source documents.

## 9.5. Prior and Concomitant Medications, Physiotherapeutic Interventions, and Lifestyle Considerations

During Screening, the subject's medical history will be collected. This will include all medications taken within 30 days of the initial Screening visit/ICF signature. If available, previous NSAA scores within 12 months of Screening will be recorded on the appropriate CRF.

All concomitant medications (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), occupational therapy, and physiotherapeutic interventions will be recorded on the eCRF from the time of informed consent/assent until the final study visit.

### 9.5.1. Corticosteroids

Subjects must be on a stable daily dose of oral corticosteroids for at least 12 weeks before the initial Screening visit, with the dose remaining constant (except for modifications to accommodate changes in weight) throughout the study. All changes to corticosteroid type, dosing frequency, the dates of start and end of corticosteroid dosage, and dosage will be recorded in the subject's source documents and on the eCRF.

#### 9.5.1.1. Pre-infusion Immunosuppressants

The day before the infusion (delandistrogene moxeparvovec or placebo), subjects will begin additional glucocorticoid (prednisone equivalent) for immunosuppression, in addition to their baseline stable oral corticosteroids for DMD. Subjects on baseline daily corticosteroid dosing for their DMD will take their usual DMD corticosteroid dose IN ADDITION to the added 1 mg/kg/day immunosuppressive dose. The 1 mg/kg/day dosing will be followed up to a total daily dose of 60 mg/day.

#### 9.5.1.2. Post-infusion Immunosuppressants

For the first 60 days following the infusion, subjects will remain on their baseline daily stable oral corticosteroid dose for DMD, and IN ADDITION will take 1 mg/kg/day of a glucocorticoid (prednisone equivalent) for immunosuppression. Earlier tapering to manage an AE may be permitted with Medical Monitor approval. The 1 mg/kg/day dosing will be followed up to a total daily dose of 60 mg/day, except for added steroids in the event of GGT increases and/or other clinically significant liver function abnormalities.

Delandistrogene moxeparvovec may cause vomiting (for details, see the Investigator's Brochure). If a subject cannot tolerate oral immunosuppressive glucocorticoids due to vomiting, then the glucocorticoids should be administered intravenously.

Post-infusion added glucocorticoid for immunosuppression should be increased if GGT level is confirmed to be ≥ 150 U/L or there are other clinically significant liver function abnormalities following infusion. The Investigator may make subsequent adjustments to immunosuppressive therapy in reaction to the subsequent course of acute liver injury or other AEs. A hepatologist must be consulted for serious or severe elevations in hepatic biochemistries (including GGT, bilirubin, and ALT relative to Baseline), or for elevations that do not respond to 2 mg/kg/day or 120 mg/day, respectively. In this situation, IV bolus steroids may be considered.

- If the subject is on 1 mg/kg of added steroid for immunosuppression in addition to their DMD steroid, this dose should be increased to 2 mg/kg of added steroid for immunosuppression to be taken in addition to their DMD steroid.
- If the subject is on 60 mg/day fixed dose, this should be increased to 120 mg/day.

Subjects with normal GGT values and no signs of acute liver injury at Day 60 should be tapered off their immunosuppressive glucocorticoid over 2 weeks. The duration of tapering may be adjusted to manage AEs, per Investigator discretion, but continuation of steroids at a dose exceeding the baseline daily regimen beyond Day 90 should be discussed with the Medical Monitor. Immunosuppressive glucocorticoids in subjects with elevated GGT values and/or signs of acute liver injury at Day 60 should be managed as above until GGT values normalize (or are clearly trending toward normal) and all signs of acute liver injury resolve, at which point they should be tapered off their immunosuppressive glucocorticoid over 2 weeks. Once the additional steroids for immunosuppression have been tapered off, they should remain on their baseline daily steroid regimen for DMD, with any required adjustment for weight.

Refer to Section 9.6.1.2 for the list of AESIs related to liver chemistry tests.

### 9.5.2. Prohibited Medications

All subjects will be asked to refrain from using concomitant medications that may interfere with the study objectives.

Prohibited medications and time frames are listed below:

CCI

- Gene therapy
- Cell-based therapy (eg, stem cell transplantation)

- CRISPR/Cas9, or any other form of gene editing

CCI [redacted]

- Use of human growth factor or givinostat

CCI [redacted]

- Any investigational medication
- Any treatment designed to increase dystrophin expression (eg, Translarna, EXONDYS 51, VILTEPSO)

Additionally, subjects should not receive live virus vaccines within CCI [redacted] or inactive vaccines within CCI [redacted] of the Day 1 visit or expect to receive vaccination during the CCI [redacted] after Day 1.

#### 9.5.3. Lifestyle Considerations

##### 9.5.3.1. Infection Precautions

For at least the first 60 days following infusion, subjects will be immunosuppressed with glucocorticoids and they should be instructed to observe standard infection precautions. These include appropriate hand washing, avoidance of sick contacts or contacts of sick contacts, avoidance of crowded settings, and use of personal protective equipment as appropriate.

## 9.6. Safety Monitoring

### 9.6.1. Safety Monitoring for Liver Chemistry Tests

Liver chemistry tests need to be monitored as specified in Section 2.3. Initial abnormal liver chemistry test result(s) needs to be confirmed if:

- GGT is CCI [redacted] or ALP CCI [redacted] × ULN or AST or ALT CCI [redacted] × Baseline excluding elevations due to muscle source

Subjects with confirmed liver chemistry test results (as above) need to have their liver chemistry tests CCI [redacted] retested CCI [redacted]. Frequency of retesting can decrease CCI [redacted] if abnormalities stabilize or delandistrogene moxeparvovec has been discontinued and the subject is asymptomatic.

#### 9.6.1.1. Additional Investigations for Liver Function

Subjects 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; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Consideration of other viral illnesses that have been associated with hepatitis (eg, Epstein-Barr virus [EBV], cytomegalovirus [CMV], Human Herpesvirus 6).
- Obtaining a history of exposure to environmental chemical agents.
- Additional liver evaluations, CCI [redacted] may be performed at the discretion of the Investigator, in consultation with the Medical Monitor.

As described in Section 9.5.1.2, a hepatologist must be consulted for serious or severe elevations in hepatic biochemistries CCI [redacted] or for elevations that do not respond to 2 mg/kg/day or 120 mg/day, respectively. In this situation, IV bolus steroids may be considered.

#### 9.6.1.2. AESIs for Liver Function

Treatment is not administered while any AESI is being evaluated or is unresolved.

CCI [redacted]

### 9.6.2. Safety Monitoring for Hypersensitivity

Subjects must be monitored for occurrence of allergic reactions primarily via monitoring AEs as specified in Section 2.3. Subjects are 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.

#### 9.6.2.1. Additional Investigations for Hypersensitivity

Subjects who experience significant or persistent constitutional symptoms need to be discussed with the Medical Monitor to determine whether additional monitoring or laboratory tests are required. Additional evaluations including CCI [redacted] may be performed at the discretion of the Investigator in consultation with the Medical Monitor.

#### 9.6.2.2. AESIs for Hypersensitivity

Treatment is not administered while any AESI is being evaluated or is unresolved.

CCI [redacted]

CCI [redacted]

### 9.6.3. Safety Monitoring for Immune-mediated Myositis

Subjects must be monitored for occurrence of immune-mediated myositis by monitoring adverse events as specified in Section 2.3. Subjects are instructed to promptly report any new muscle pain, tenderness, or weakness, including dysphagia, dyspnea, or hypophonia as these may be symptoms of myositis and the Investigator needs to closely evaluate all potential causes, including concomitant illness and underlying disease.

#### 9.6.3.1. Additional Investigations for Immune-mediated Myositis

Reports of rapidly progressing muscular weakness need to be discussed with the Medical Monitor to determine whether additional monitoring or laboratory tests are required.

Additional evaluations including CCI [redacted] may be performed at the discretion of the Investigator in consultation with the Medical Monitor.

#### 9.6.3.2. AESIs for Immune-mediated Myositis

CCI [redacted]

### 9.6.4. Safety Monitoring for Thrombotic Microangiopathy (TMA)

Subjects must be monitored for occurrence of complement-mediated reactions primarily via monitoring AEs and complement levels. Subjects are 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 alternative causes, including concomitant illness or medications. In addition to monitoring AEs, routine laboratory monitoring for complement-mediated reactions is performed per protocol as specified in Section 2.3, including complement levels (CCI [redacted], C3, C4, and CCI [redacted]).

#### 9.6.4.1. Additional Investigations for TMA

Reports of TMA need to be discussed with the Medical Monitor to determine additional monitoring and laboratory testing. Additional evaluations including CCI [redacted] may be performed at the discretion of the Investigator in consultation with the Medical Monitor.

#### 9.6.4.2. AESIs for TMA

CCI [redacted]

### 9.6.5. Safety Monitoring for Platelet Count Results

The platelet count needs to be monitored as specified in Section 2.3. Subjects who have a confirmed occurrence of platelets CCI [redacted] need to have the following evaluations performed:

CCI [redacted]

#### 9.6.5.1. Additional Investigations for Platelet Count

Additional platelet evaluations for confirmed, unexplained significant platelet count reductions, including CCI [redacted] may be performed at the discretion of the Investigator in consultation with the Medical Monitor.

#### 9.6.5.2. AESIs for Platelet Count

Treatment is not administered while any AESI is being evaluated or is unresolved.

CCI [redacted]

### 9.6.6. Safety Monitoring for Rhabdomyolysis

Rhabdomyolysis must be monitored by urine dipstick and adverse events as specified in Section 2.3. Subjects who have confirmed heme+ dipstick urinalysis need to be evaluated for urine microscopy and the following adverse events:

CCI [redacted]

#### 9.6.6.1. Additional Investigations for Rhabdomyolysis

In case of rhabdomyolysis, myoglobinuria or chromaturia, subjects need to have evaluations of CCI these evaluations should be undertaken at the discretion of the Investigator. In addition, Investigators obtain a more detailed history of symptoms, preceding activity and hydration status, concomitant drug use, and recent or concurrent infections. Additional evaluations, including CCI may be performed at the discretion of the Investigator in consultation with the Medical Monitor. If acute onset or exacerbation of weakness is a feature of the rhabdomyolysis event, the subject is assessed for rapidly progressive weakness.

#### 9.6.6.2. AESIs for Rhabdomyolysis

Treatment is not administered while any AESI is being evaluated or is unresolved.

CCI

#### 9.6.6.3. Risk of Rhabdomyolysis due to Anesthesia

Participation in this study involves biopsies which may require anesthesia (Section 10.3.3). Investigators should be aware that patients with DMD have specific risks and requirements when undergoing anesthesia (American Academy of Pediatrics 2005, Birnkrant 2009, Bushby 2010). For example, there is an absolute contraindication against the use of depolarizing muscle relaxants (eg, succinylcholine, also known as suxamethonium) due to the risk of rhabdomyolysis; and a strong recommendation to avoid inhalational anesthetics (eg, sevoflurane, desflurane, enflurane, halothane, isoflurane) due to the risk of malignant hyperthermia-like reactions and rhabdomyolysis. There is no evidence that exposure to delandistrogene moxeparvovec affects these risks. For more details regarding anesthesia required during biopsies, refer to the Biopsy Surgical and Laboratory Manual.

### 9.6.7. Safety Monitoring for Troponin Increased/Myocarditis

Cardiac troponin levels need to be monitored as specified in Section 2.3. Initial cardiac troponin level result needs to be confirmed if:

- Cardiac troponin levels CCI × ULN (or CCI Baseline for subjects with elevated baseline values)
- Subjects with confirmed abnormal cardiac troponin levels need to have their cardiac troponin levels retested until the level returns to Baseline or stabilizes for at least CCI. Frequency of retesting is at the discretion of the Investigator.

- Acute chest pain or pressure, palpitations, dyspnea after exercise, at rest or lying down, diaphoresis, and sudden death
- Dizziness or syncope, edema, and vomiting, especially severe vomiting or presence of 2 and more symptoms
- For infants and children, irritability, vomiting, poor feeding, tachypnea, and lethargy

#### 9.6.7.1. Additional Investigations for Troponin Increased/Myocarditis

Additional evaluations including CCI [redacted] may be performed at the discretion of the Investigator in consultation with the Medical Monitor.

#### 9.6.7.2. AESIs for Troponin Increased/Myocarditis

CCI [redacted]

## 9.7. Treatment Overdose

For this study, any dose of delandistrogene moxeparvovec above CCI [redacted] will be considered an overdose. CCI [redacted] In the event of an overdose, the Investigator should:

1. Contact the unblinded CRO Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until resolution.
3. Document the quantity of the excess dose on the Clinical Trial Safety Reporting Form and send to the Sponsor immediately. The overdose should also be entered in the eCRF.
4. Provide appropriate medical care to the subject based on clinical judgement.

Decisions regarding additional subject monitoring will be made by the Investigator in consultation with the unblinded CRO Medical Monitor based on the clinical evaluation of the subject.

An overdose must be reported to the Sponsor or designee using the Clinical Trial Safety Reporting Form within 24 hours of the Investigator's first knowledge of the event, even if the overdose does not result in an AE, according to the process for reporting SAEs (Section 11.4.1 ).

# 10. STUDY ASSESSMENTS

## 10.1. Schedule of Events

The schedule outlining the study assessments and times of assessments is shown in Section 2.3.

## 10.2. Screening/Baseline Assessments

### 10.2.1. Informed Consent and Assent

Informed consent from the parent(s)/legal guardian(s) and assent from the subject (if applicable) to participate in this study must be obtained prior to performing any of the procedures required for this study.

### 10.2.2. Demographic/Medical History

Demographic information (eg, age, gender at birth, race, ethnicity, body weight, height, body mass index) and medical history will be obtained for all subjects.

### 10.2.3. Genetic Diagnostics

Subjects must have a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop, or other pathogenic variant in the *DMD* gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein.

a. Mutations between or including exons 1 to 17 are not eligible.
b. In-frame deletions, in-frame duplications, and variants of uncertain significance ("VUS") are not eligible.
c. Mutations that are fully contained within exon 45 (inclusive) are not eligible.

## 10.3. Efficacy Assessments

### 10.3.1. Functional Assessments

Every effort must be made to have each subject assessed by the same clinical evaluator for physical functional assessments (NSAA and timed-function tests) throughout the entire study. Functional assessments should be scheduled in the morning and should be the first assessments done during a specific visit. As NSAA is the primary outcome measure, it is to be performed first, followed by the timed-functional tests. Physical functional assessments are to be performed CCI [redacted] throughout the study. Every effort should be made for the same assessor to perform the assessments throughout the study for a subject.

If assessments that would impact the primary and/or secondary objectives cannot be performed due to events not reasonably foreseen for a period of time longer than CCI [redacted], these assessments may be performed remotely where applicable. The subject should return to the clinic as soon as possible to perform the assessment in person, unless CCI [redacted] of the next protocol scheduled assessment as applicable.

Functional assessments will be administered at the time points indicated in Section 2.3.

Refer to the Clinical Evaluator Manual for additional information.

#### 10.3.1.1. North Star Ambulatory Assessment

The NSAA is a clinician-administered scale that rates performance on various functional activities (Mazzone 2010). It was designed to be used in boys with DMD who are able to stand, and it has been used in DMD boys of this study's age range (≥ 4 and < 8 years) (Connolly 2013, Mercuri 2016).

During this assessment, subjects perform 17 different functional activities, including the 10MWR, rising from a sit to a stand, standing on 1 leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor, lifting head off floor, standing on heels, and jumping.

Subjects 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.

Details on administration of the NSAA are provided in the Clinical Evaluator Manual.

Two NSAA scores will be collected CCI [redacted] at Baseline, CCI [redacted] at Week 52 in Part 1, CCI [redacted].

##### 10.3.1.1.1. Time to Rise from the Floor

The time to rise from the floor test is part of the NSAA (item 12) and quantifies the time required for the subject to stand in an upright position with arms by sides, starting from the supine position with arms by sides (Henricson 2013). The time required for the subject to complete the task will be recorded during the NSAA administration. As with NSAA, the time to rise from the floor will be collected CCI [redacted].

##### 10.3.1.1.2. 10-Meter Walk/Run

The timed 10MWR is part of the NSAA (item 17) and quantifies the time required for the subject to run or walk 10 meters (on a straight walkway) from a standing position (McDonald 2013). The subject is encouraged to run past the 10-meter mark. The time required for the subject to cover the distance will be recorded during the NSAA administration. As with NSAA, timed 10MWR will be collected CCI [redacted].

#### 10.3.1.2. Time to Ascend 4 Steps

The timed 4-step test quantifies the time required for the subject to ascend 4 standard steps (each step 6 inches in height) (Bushby 2011). The time required for the subject to climb up 4 standard-sized steps will be recorded.

#### 10.3.1.3. 100-Meter Walk/Run

The 100MWR quantifies the time required for the subject to run or walk 100 meters (on a straight walkway) from a standing position (Alfano 2017). The subject is encouraged to run past the 100-meter mark. The time required for the subject to cover the distance will be recorded.

### 10.3.2. Wearable Device

Subjects will be provided with a wearable device to collect daily physical activities. The purpose of the wearable device is to accurately measure the movement and activity levels of the subject during normal daily living, outside of investigational site visits. CCI [redacted] As the wearable device battery requires recharging daily after use, the sensors will not be worn at night. Site personnel, the subject, and parents/caregivers will be trained on the correct use of the device. Detailed user instructions are provided in the Wearable Investigator Manual.

During the Pre-infusion Period, subjects should attempt to wear the device CCI [redacted] to capture baseline values. During the Follow-up Period, subjects should attempt to wear the device CCI [redacted]. The wearable device will not be worn during clinic visits, but subjects will resume use immediately following completion of in-clinic tests. Subjects must return the wearable device in the event of screen failure, early termination, or after study completion. Refer to the Wearable Investigator Manual for additional information.

### 10.3.3. Delandistrogene Moxeparvovec Dystrophin Expression

CCI [redacted]

The biopsy sample will be used to quantify delandistrogene moxeparvovec dystrophin protein expression by Sarepta's western blot adjusted for muscle content, CCI [redacted]. Refer to the Biopsy Surgical and Laboratory Manual for additional details on the handling and processing of biopsy tissues.

CCI [redacted]

CCI [redacted]

#### 10.3.6.1. Patient-Reported Outcomes Measurement Information System

A subset of subjects based on regional availability will complete the PROMIS measures; participating countries will be outlined in the Study Operations Manual.

PROMIS is a family of instruments developed and validated to assess health-related quality of life (PROMIS 2018, Bevans 2010). PROMIS measures have been developed in alignment with the Food and Drug Administration's methodological standards for the assessment of patient-reported outcomes (Bevans 2010, FDA 2018) and are comprised of person-centered items that evaluate and monitor physical, mental, and social health in adults and children. Specific measures for child outcomes in this study will include the following proxy measures:

- PROMIS Parent Proxy Item Bank V2.0 - Mobility - (23 items)
- PROMIS Parent Proxy SF V2.0 – Upper Extremity – Short Form 8a (8 items)

CCI [redacted]

If a subject turns 8 years old within the study period, the following Pediatric PROMIS measures will also be administered and completed by the subject. The parent/caregiver will continue to complete the proxy measure.

- PROMIS Pediatric Item Bank V2.0 - Mobility (24 items)
- PROMIS Pediatric Item Bank V2.0 - Upper Extremity - Short Form 8a (8 items)

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

## 10.4. Safety Assessments

### 10.4.1. Adverse Events

The collection of AEs is detailed in Section 11.2.

### 10.4.2. Demographic/Medical History

Demographic data and medical history will be collected at the Screening visit.

### 10.4.3. Vital Signs Measurements, Weight, and Height

Vital sign measurements (including blood pressure, heart rate, respiratory rate, and oral/tympanic/axillary temperature), height and weight will be obtained at the time points specified in Section 2.3.

During the study, vital signs will be collected from the contralateral arm from which the blood samples are collected. On Day 1, vital signs will be measured at CCI minutes prior to the start of infusion and at the following timepoints after the start of infusion:

CCI

All vital sign measurements will be performed after the subject has remained inactive and supine for at least 5 minutes. Pulse rate and respiratory rate will be measured over 1 minute.

When vital sign assessments are scheduled to be collected at the same time as blood draws, the vital signs will be measured prior to, but as close to, the scheduled time of the blood draw as possible.

Temperature will be recorded in degrees Celsius; weight is to be recorded in kilograms, and height and ulnar length is to be recorded in centimeters.

### 10.4.4. Physical Examination

A full or brief (symptom-directed) physical examination will be performed by the Investigator or qualified study staff at the time points specified in Section 2.3.

Full physical examinations will include examination of general appearance, head, ears, eyes, nose, throat (HEENT), heart, chest (respiratory), abdomen (gastrointestinal), skin, lymph nodes, extremities, and the musculoskeletal and neurological systems.

A brief physical examination will include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

### 10.4.5. Electrocardiograms and Echocardiograms

A 12-lead ECG will be obtained in triplicate at the time points specified in Section 2.3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. All ECGs should be performed at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). All ECGs should be performed only after the subject is in the supine position, resting, and quiet for approximately 15 minutes. On Day 1, triplicate ECGs will be taken both before and following the end of the infusion. The Investigator or designee will review the ECG results and determine if the findings are clinically significant. The Day 1 pre-infusion review should be completed and documented prior to study drug infusion.

A standard 2-dimensional ECHO will be obtained at the time points specified in Section 2.3. Echocardiograms are to be performed at a consistent time of day for each assessment throughout the study and before any invasive procedures (eg, blood sampling, study drug infusion, or biopsy). The ECHO will be reviewed and interpreted by local medically qualified personnel. Left ventricular ejection fraction will be noted.

### 10.4.6. Laboratory Assessments

#### 10.4.6.1. Routine Clinical Laboratory Tests

The following routine clinical laboratory tests will be performed at the time points specified in Section 2.3. Results will be processed according to the Laboratory Manual provided and analyzed by a central laboratory. If local regulations restrict the blood volume further than what is outlined in the Investigator's Laboratory Manual, the Investigator should consult with the Medical Monitor in order to determine prioritization.

Where applicable, CCI [redacted] may be performed remotely (Section 2.3 and Section 10.3.1). This is intended to reduce study burden while maintaining ongoing in-person surveillance by the study site. Detailed instructions for remote visits will be provided in the Investigator's Laboratory Manual.

If hepatic and platelet monitoring laboratories scheduled within the first CCI [redacted] are unable to be performed at the central laboratory due to events not reasonably foreseen, these assessments may be performed remotely and/or at local laboratories where applicable. In addition, if any laboratory assessments that impact AE management cannot be performed at the central laboratory, these assessments may be done locally at the discretion of the caregiver.

Note: At CCI, samples will be collected CCI.

| | |
|---|---|
| Electrolytes: | Sodium, chloride, potassium, carbon dioxide |
| Troponin: | Troponin I |
| Glucose: | Serum glucose |
| CCI | CCI |
| Liver Function: | Total and direct bilirubin, alkaline phosphatase, amylase, ALT, AST, GGT, lactate dehydrogenase, albumin. Additionally, GLDH is collected for research use only. |
| Hematology: | Red blood cells, total white blood cells, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, prothrombin time, partial thromboplastin time, INR |
| hsCRP and complement: | hsCRP and complement (CCI, C3, C4, CCI) |
| Renal function: | Creatinine, blood urea nitrogen, and serum cystatin C |
| Urinalysis: | pH, specific gravity, protein, glucose, ketones, hemoglobin |

Any value outside of the reference ranges for the laboratory performing the test will be flagged in the laboratory results. The Investigator or designee will determine whether abnormal results are clinically significant.

A laboratory abnormality (Section 11.2.1) deemed clinically significant by the Investigator or designee should be recorded as an AE. A clinically significant abnormality is generally an abnormality, confirmed by repeat testing, that is changed sufficiently from Screening/Baseline so that, in the judgment of the Investigator, a change in management is warranted.

CCI

CCI [redacted]

**Sample Collection**

CCI [redacted]

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

CCI samples are to be stored until they are no longer needed or until they are exhausted. However, the CCI storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (eg, health authority requirements).

#### 10.4.6.3. Virus Serology

Blood samples will be collected at the Screening visit for analysis of HIV, hepatitis B, and anti-hepatitis C virus testing. Hepatitis B results will be based on the United States, Department of Health & Human Services, Centers for Disease Control and Prevention, Interpretation of Hepatitis B Serologic Test Results (Department of Health and Human Services 2005).

Blood samples will be collected at the Baseline visit for analysis of EBV, CMV, parvovirus B19, varicella zoster virus, HH6, hepatitis A, and hepatitis E.

#### 10.4.6.4. Concomitant Medications and Physiotherapeutic Interventions

New and ongoing concomitant medications and procedures, changes in dosage of concomitant medications, and concomitant therapies, including physiotherapeutic interventions, will be reviewed, and recorded at each visit from the time the subject signs the informed consent/assent form through the end of the study. See Section 9.5 for details of permitted concomitant medications.

CCI [redacted]

### 10.4.8. Use/Analysis of Muscle Biopsies

In addition to the analyses listed in Section 10.3.3 and Section 10.3.4, the use/analysis of muscle biopsies is outlined below:


- The results of muscle biopsy analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the muscle biopsy samples in a secure storage space with adequate measures to protect confidentiality.
- All samples obtained will be stored for CCI and maintained for up to CCI following the end of the study or in accordance with local regulation if permitted by the informed consent/assent form.


CCI

# 11. ADVERSE EVENTS AND OTHER SAFETY INFORMATION

## 11.1. Definitions

### 11.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject that does not necessarily have a causal relationship with the study drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

Adverse events include:

- Symptoms described by the subject or signs observed by the Investigator or medical staff
- The onset of new illness and the exacerbation of pre-existing medical conditions
- Test abnormalities (laboratory tests, ECG, etc.) deemed clinically significant

Abnormalities present at Screening will be collected as part of medical history and are considered AEs only if they re-occur after resolution or worsen during the AE collection period.

### 11.1.2. Serious Adverse Event

A Serious Adverse Event (SAE) is an untoward medical occurrence that at any dose:

- Results in death
- Is life threatening

  **Note:** The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization **
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

  **Note:** Medical and scientific judgment should be exercised in deciding whether an event should be reported as an SAE in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

**Sponsor Note on Hospitalizations**

The following types of hospitalizations do not meet the SAE criteria defined above:

- Hospitalizations that are part of the study procedures unless the hospitalization is prolonged (based on the judgment of the Investigator) due to an AE
- Elective or pre-planned hospitalizations for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form (documented as medical history on the eCRF if applicable per protocol)

### 11.1.3. Suspected Unexpected Serious Adverse Reactions

A Suspected Unexpected Serious Adverse Reactions (SUSAR) is an AE or suspected adverse reaction considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

### 11.1.4. Adverse Event of Special Interest

An AESI is any AE (serious or nonserious) that is of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted. A list of AESIs is presented in Section 11.4.2.5.

### 11.1.5. Special Situations

A comprehensive term that encompasses safety information related to products for which global regulations require collection, evaluation, and/or reporting to regulatory authorities.

Special situations include, but are not limited to, reports of:

- Overdose: Whether accidental or intentional, with or without any AEs. Administration of a quantity of a study drug given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. See Section 9.7 for further details.
- Medication error: Actual and potential, including product confusion. An unintended failure in the study drug treatment process that leads to, or has the potential to lead to, harm to the subject (see EMA-PRAC Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors, 23 October 2015).
- Product misuse: Situations where a study drug is intentionally and inappropriately used not in accordance with the terms of the Investigator's Brochure.
- Product abuse: Abuse of a study drug that is persistent or sporadic; intentional excessive use of study drug, which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

- Occupational exposure: For the purpose of reporting cases of suspected adverse reactions, an exposure to a study drug as a result of one's professional or non-professional occupation.
- Drug interactions: Occur when 2 or more drugs react with each other. Drug-drug interaction may cause an unexpected side effect experience.
- Unexpected benefit: Unanticipated desirable and beneficial effects resulting from a medical treatment aside from the use for which it has been given.
- Accidental exposure: Inadvertent exposure to the medicinal product by someone other than the subject.

## 11.2. Collection of Adverse Events

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be collected, and documented in the eCRF.

All AEs will be collected and recorded from the time of informed consent/assent through the last follow-up visit.

All AEs (including AESIs and special situations) and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to stabilization, baseline status, and there is a satisfactory explanation for the changes observed, completion of the subject's study participation, or study termination, whichever occurs first.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the treatment period. Pre-existing conditions must be recorded in the eCRF, as well as on the Clinical Trial Safety Reporting Form's medical history section.

For subjects who are prematurely discontinued from the study (Section 8.5), AEs should continue to be recorded at least until 28 days after the last study drug administration.

For subjects who are found to be ineligible for the study during the Pre-infusion Period and are not enrolled (ie, screen failures), only SAEs (Section 11.1.2) will be reported (Section 11.4.1).

If, at any time after the subject has completed participation in the study (Section 8.4), the Investigator or study staff become aware of an SAE that the Investigator assesses as related to the study drug (Section 11.3.1) or related to a study procedure (Section 11.3.2), then the event and any known details must be reported promptly to the Sponsor, no later than within 24 hours of awareness.

### 11.2.1. Clinical Laboratory Abnormalities

A laboratory abnormality deemed clinically significant (Section 10.4.6.1) by the Investigator should be recorded as an AE. A clinically significant abnormality is generally an abnormality, that is changed sufficiently from Screening/Baseline in the judgment of the Investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE (if it meets seriousness criteria), and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome,

only the diagnosis needs to be recorded on the Clinical Trial Safety Reporting Form and eCRF. Abnormal laboratory values assessed as not clinically significant should be documented as such in the source document.

### 11.2.2. Disease Progression

Disease progression *per se* is not to be reported as an AE in this study. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per the AE/SAE reporting requirements described in this section.

## 11.3. Classification of Adverse Events

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

### 11.3.1. Relationship to Study Drug

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

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

### 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. |

### 11.3.4. Severity of Adverse Events

The Investigator will assess the severity of all AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 5.0. Adverse events not listed in the CTCAE will be assessed according to the following scale.

**Grade 1 Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

**Grade 2 Moderate:** minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL

**Grade 3 Severe or medically significant but not immediately life-threatening:** hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

**Grade 4 Life-threatening consequences**: urgent intervention indicated

**Grade 5 Death** related to AE

Note that severity is not the same as "seriousness," which is defined in Section 11.1.2 and which serves as a guide for defining regulatory reporting obligations.

In addition, laboratory or vital signs-based AEs that are defined as Grade 4 in the CTCAE ***solely by laboratory or vital sign measurements*** are not automatically clinically life-threatening; the Investigator must make this clinical assessment regardless of grade. All other AEs of Grade 4 (life-threatening) or Grade 5 (fatal) severity are to be reported as SAEs (Section 11.4.1).

### 11.3.5. Outcomes of Adverse Events

"Outcome" describes the status of the AE. The Investigator will provide information regarding the subject outcome for each AE. Outcome categories will include "recovered", "recovered with sequelae", "not recovered", "fatal", and "unknown."

### 11.3.6. Action Taken Regarding the Study Drug

The Investigator will provide information regarding the action taken with respect to the study treatment in response to the AE. Categories for action taken regarding study treatment will include "none" and "drug interrupted."

### 11.3.7. Expectedness of Adverse Events

The expectedness of all AEs will be determined by the Sponsor according to the most recent version of the Reference Safety Information (RSI) section of the Investigator's Brochure for delandistrogene moxeparvovec. Expectedness is defined as whether an AE is listed or not listed in the RSI section of the Investigator's Brochure.

## 11.4. Recording of Adverse Events

All AEs, from the signing of informed consent/assent through the last Follow-up visit, will be recorded in each enrolled subject's eCRF. All SAEs and other safety information, such as that pertaining to special situations (Section 11.1.5) including specified AESIs (Section 11.4.2.5) will also be recorded on the Clinical Trial Safety Reporting Form and reported to the Sponsor via email to PPD within 24 hours of awareness. Electronic reporting may be

configured for this study; when configured and deployed, the Sponsor will receive safety information recorded in the subjects' eCRF via a CCI [redacted].

Information recorded should include the following: a concise description of the AE; date of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to study drug, study procedure, and underlying disease; any action taken, relevant laboratory results, and diagnostic tests. Resolution occurs when the subject has returned to the Baseline state of health, or when further improvement or worsening of the AE is not expected.

If a diagnosis is known at the time of reporting, the diagnosis should be recorded as an AE, rather than its signs and symptoms or isolated laboratory abnormalities related to that diagnosis. Several symptoms or laboratory results that are associated with 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. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up and should replace the individual signs and/or symptoms as the event term on the eCRF.

Similarly, death is not an AE, but rather, the outcome of the AE(s) that resulted in death. 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, the best MedDRA Preferred Term to describe the death will be recorded as the AE.

Any SAE assessed as related to the study drug, occurring after the subject completes the study, should be recorded on a Clinical Trial Safety Reporting Form, and reported as per the instructions for SAEs provided immediately below.

### 11.4.1. Reporting Serious Adverse Events

#### 11.4.1.1. Serious Adverse Events

All SAEs, from the signing of informed consent/assent through the last Follow-up visit, including SAEs from screen failures, will be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event.

| | | |
|---|---|---|
| Email: PPD | US Fax: PPD | EU Fax: PPD |

Serious AEs should be communicated on the Clinical Trial Safety Reporting Form as follows: The initial report must be completed as soon as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the study drug(s). Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be provided to the Sponsor during Follow-up. All follow-up information must be reported in the same timelines as the initial information. At any time after completion of the AE reporting period (ie, after last Follow-up visit), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to study drug, the event must be reported to the Sponsor or designee.

The Sponsor may request follow-up information on a PV query form or send targeted questionnaires to collect additional information.

#### 11.4.1.2. Suspected Unexpected Serious Adverse Reactions

All SUSARs will be handled by appropriate Sponsor (or designee) personnel and reported within the required timelines, in an unblinded fashion, to regulatory authorities and the IRB/IEC, per ICH and local regulations and/or the requirements of the concerned competent authorities.

### 11.4.2. Reporting Special Situations

Regardless of whether or not there is an associated AE, special situations will be collected as part of the study drug dosing information and/or as a protocol violation, as required.

Any AEs associated with the special situations should be recorded on the AE eCRF with the diagnosis of the AE.

#### 11.4.2.1. Overdose

Refer to Section 9.7 for the definition of treatment overdose. 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 Clinical Trial Safety Reporting Form and sent to the Sponsor or designee within 24 hours according to the process for reporting SAEs (Section 11.4.1).

#### 11.4.2.2. Medication Error

Any medication error is to be reported to the Sponsor on the Clinical Trial Safety Reporting Form within 24 hours of awareness of the error even if the error does not result in an AE, according to the process for reporting SAEs (Section 11.4.1).

#### 11.4.2.3. Accidental/Occupational Exposure

Any accidental/occupational exposure (Section 11.1.5) is to be reported to the Sponsor on the Clinical Trial Safety Reporting Form within 24 hours of becoming aware, according to the process for reporting SAEs (Section 11.4.1).

#### 11.4.2.4. Product Misuse/Abuse

Any misuse/abuse (Section 11.1.5) are to be reported to the Sponsor on the Clinical Trial Safety Reporting Form within 24 hours of becoming aware, according to the process for reporting SAEs (Section 11.4.1).

#### 11.4.2.5. Adverse Events of Special Interest

All AESIs are immediately reportable events, even if the events do not meet SAE criteria. This includes the events below that are based on laboratory abnormalities, which should be translated to the appropriate AE term at the time of reporting.

All AESIs should be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, whether or not the event is serious, even if the experience does not appear to be related to the study drug. AESIs should be reported as described above for SAEs, according to the process for reporting SAEs (Section 11.4.1).

In this study, the following AEs are considered AESIs:

Hepatotoxicity

CCI [redacted]

Myositis

CCI [redacted]

Thrombotic microangiopathy (TMA)

CCI [redacted]

Hypersensitivity

CCI [redacted]

Thrombocytopenia

CCI [redacted]

Rhabdomyolysis

CCI [redacted]

Troponin elevations

CCI [redacted]

### 11.4.3. Miscellaneous

#### 11.4.3.1. Responsibilities of the Investigator

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

- Monitoring and recording all AEs
- Determining the seriousness, severity, and relationship to study drug, study procedure, and underlying disease for each AE
- Determining the onset and end date of each AE
- Providing the initial report of all SAEs, special situations, and noted AESIs to the Sponsor via email to PPD or designee within 24 hours of first knowledge.
- 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
- Submission of safety events to the IEC/IRB according to the policies and requirements

Investigators may also report improvement of pre-existing DMD conditions or unexpected therapeutic responses.

#### 11.4.3.2. Responsibilities of the Sponsor

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

- Training of Investigator on AE/SAE, special situations and AESI definitions, safety assessments, and site obligations related to safety monitoring and reporting of AEs/SAEs
- Training with regard to the accurate and legal reporting of SAEs to all applicable regulatory authorities, IRBs/IECs, clinical study sites, and other parties, as appropriate and required within the regulated timing
- Ensuring accurate recording of AEs and SAEs, Special Situations, and AESIs
- Submission of expedited serious, unexpected, and related AEs to regulatory authorities per regulatory requirements
- Notification of blinded, unexpected and related SAEs to sites
- Annual safety reporting to regulatory authorities and IRBs/IECs according to regional requirements

# 12. STATISTICAL CONSIDERATIONS

## 12.1. Statistical Hypotheses

For the primary efficacy endpoint of change in NSAA total score from Baseline to Week 52 (Part 1), the null hypothesis is that the population means for the 2 treatments are equal and the alternative hypothesis is that the population means for the 2 treatments are not equal. Even though the alternative hypothesis is 2-sided, only superiority of delandistrogene moxeparvovec over placebo will be of interest.

The statistical hypotheses for secondary efficacy endpoints can be stated in a similar manner as those for change in NSAA total score from Baseline to Week 52 (Part 1).

## 12.2. Sample Size Determination

The sample size of this study is based on the power for the primary efficacy endpoint, change in NSAA total score from Baseline to Week 52 (Part 1).

CCI [redacted]

This sample size calculation CCI [redacted] is based on efficacy data from a double-blind, placebo-controlled, Phase 2 study as well as comparison against external controls in DMD.

## 12.3. Analysis Populations

For purposes of statistical analyses, the following analysis populations are defined:

| Population | Description |
|---|---|
| Intent-to-Treat (ITT) | All randomized subjects (not including those enrolled under a regional addendum), with treatment group designated according to randomization. |
| Modified Intent-to-Treat (mITT) | All randomized subjects who receive study treatment (not including those enrolled under a regional addendum), with treatment group designated according to randomization. The mITT population will be the analysis population for efficacy endpoints. |
| Safety | All subjects who received study treatment (not including those enrolled under a regional addendum), with treatment group designated according to the treatment that they actually received. |

## 12.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the primary and secondary efficacy endpoints as well as the safety analyses. Details of the statistical analyses will be included in the SAP, which will be developed and finalized before database lock and unblinding of the study data.

### 12.4.1. Subject Disposition

The number and percentage of subjects completing or prematurely discontinuing from the study will be summarized by treatment. Reasons for premature discontinuation will also be summarized. The analyses will be based on the mITT population.

### 12.4.2. Demographic and Baseline Characteristics

Demographic information and baseline characteristics including age (years), sex at birth, race, ethnicity, baseline height (cm), weight (kg), body mass index ($kg/m^2$), genetic mutations, and prognostic factors such as baseline measures for functional assessments will be summarized by treatment. The analyses will be based on the mITT population.

### 12.4.3. Concomitant Medications

Concomitant medications will be coded by preferred term (PT) using the most recent World Health Organization Drug Dictionary (WHODrug) version. The number and percentage of subjects in the mITT population with concomitant medications will be tabulated by Anatomical Therapeutic Chemical classification pharmacological subgroup and WHODrug PT.

### 12.4.4. Efficacy Analyses

The primary endpoint and some secondary endpoints will be tested in a hierarchical manner using an appropriate multiple testing approach that provides strong control of the familywise Type 1 error rate at a 2-sided 0.05 level. The details of the testing procedure will be specified in the SAP.

#### 12.4.4.1. Analyses of Primary Efficacy Endpoint

For the primary endpoint of change in NSAA total score from Baseline to Week 52 (Part 1), summary statistics will be provided by treatment group for NSAA total score at Baseline, each post-Baseline visit in Part 1, and for change from Baseline to each post-Baseline visit in Part 1.

CCI [redacted]

As the primary analysis, a restricted maximum likelihood-based mixed model repeated measures analysis will be used to compare the 2 treatment groups for change in NSAA total score from Baseline to Week 52 (Part 1). In this model, the response vector consists of the change in NSAA total score from Baseline to each post-Baseline visit in Part 1. The model will include the covariates of treatment group (categorical), visit (categorical), treatment group by visit interaction, age group at randomization, baseline NSAA total score, age group at the time of randomization by visit interaction, and baseline NSAA total score by visit interaction. All covariates will be fixed effects in this analysis.

An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure results in a lack of convergence, the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom (Kenward 1997). In the primary analysis, missing data are assumed to be missing at random.

Sensitivity analyses will be performed to assess the robustness of the primary analysis conclusions with respect to deviations from missing at random assumption.

CCI [redacted]

#### 12.4.4.2. Analyses of Key Secondary Endpoints

The following secondary endpoints will be analyzed using similar statistical methods as the primary endpoint, as appropriate, with details specified in the SAP:

- Number of skills gained or improved at Week 52 (Part 1) as measured by the NSAA
- Change in timed function tests, including the rise from the floor, the 100MWR, time to ascend 4 steps, and the 10MWR from Baseline to Week 52 (Part 1)
- Change in SV95C from Baseline to Week 52 (Part 1)
- Change in PROMIS score in Mobility domain and Upper Extremity Function domain from Baseline to Week 52 (Part 1)

For the secondary endpoint of quantity of delandistrogene moxeparvovec dystrophin protein expression at Week 12 (Part 1) as measured by western blot of biopsied muscle tissue, summary statistics will be provided by treatment group for delandistrogene moxeparvovec dystrophin protein expression at Week 12 (Part 1). A re-randomization test will be performed to compare the endpoint between the 2 treatment groups.

The superiority of delandistrogene moxeparvovec over placebo will be concluded if the test achieves statistical significance based on the multiplicity-adjusted testing procedure that will be specified in the SAP.

### 12.4.5. Safety Analyses

#### 12.4.5.1. Adverse Events

All safety analyses will be based on the safety population.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. A TEAE will be defined as an AE that emerges during treatment, having been absent pre-treatment, or worsens relative to the pretreatment state. A drug-related TEAE will be defined as a TEAE that the Investigator considers related to study drug.

Treatment-emergent adverse events and drug-related TEAEs will be summarized separately by treatment group by the number and percentage of subjects who reported TEAEs. Safety analyses for each study period will use all visits up through the last scheduled visit in the prior study period as baseline. For each subject and TEAE, the maximum severity for the MedDRA level being displayed (preferred term, High Level Term, or system organ class [SOC]) is the

maximum post-baseline severity observed from all associated terms mapping to that MedDRA level.

Serious adverse events, and treatment-emergent SAEs separately, will be summarized by treatment group.

#### 12.4.5.2. Other Safety Assessments

Descriptive statistics for ECG, vital signs, immunogenicity, and safety laboratory parameters will be generated. Summary statistics for each parameter at specific time points, as well as the change from Baseline to that time point (if applicable), will also be displayed. All safety data will be presented in the data listings.

## 12.5. Interim Analysis

The primary analysis of the study will be performed after all subjects have completed Part 1 or have withdrawn early from Part 1. No interim analysis is planned prior to the completion of Part 1.

## 12.6. Data Monitoring Committee

A program-wide independent Data Monitoring Committee (DMC) will monitor safety, efficacy, data quality, and the integrity of study. The activities and composition of this committee are outlined in the DMC Charter.

# 13. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

## 13.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

The Investigator(s)/institution(s) agree to provide direct access to source data/documents (including electronic records, unless prohibited by local regulations) for study-related monitoring, audits, IRB/IEC review, and regulatory inspections.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

1. Provide information and support to the Investigator(s)
2. Confirm that facilities remain acceptable
3. Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that study drug accountability checks are being performed
4. Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
5. Record and report any protocol deviations not previously sent to the Sponsor.
6. Confirm AEs and SAEs have been properly documented on case report forms and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC as required.

The monitor will be available between visits if the Investigator(s) or other staff need information or advice.

## 13.2. Recording of Data

Clinical data for this study will be captured in an electronic format. The Investigator, or personnel delegated by the Investigator, will perform primary data collection/perform assessments based on the protocol design and captured in source documentation. Source documents are filed at the Investigator's site. All required study information must be recorded on the appropriate eCRF screens/forms. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents. All data must be carefully entered in a timely fashion to permit meaningful interpretation and study oversight.

## 13.3. 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 Clinical Monitoring Plan against the source documentation for identification and clarification of any discrepancies. The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. 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 site staff to resolve. All changes to the eCRFs will be tracked in an electronic audit trail. Investigator site 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, subject medical records, and other source documentation, study drug dispensing records and 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.

## 13.4. Retention of Study Documents

At CSR completion, all eCRF data for an individual site will be provided via electronic media to the Investigator for retention in the Investigator site files.

The length of storage of study documents varies by country and stage of clinical development in any region in the world. Therefore, no study documents, including subject records and other source data, 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 are to be transferred to an agreed-upon designee.

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

# 14. ETHICS AND OTHER SPECIAL REQUIREMENTS

It is the responsibility of both the Sponsor and the Investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, GCP Guidelines described in the ICH E6 (R2) and 21 Code of Federal Regulations parts 50, 54, 56, and 312; and applicable national regulations and directives such as EU Clinical Practice Directive 2005/28/EC, Regulation EU No 536/2014, Japanese GCP Regulation, and other applicable regulatory requirements. The clinical study will be conducted in compliance with Pharmaceutical and Medical Device Act, and the Clinical Study Protocol.

## 14.1. Institutional and Ethics Review

Before study initiation, the protocol, Investigator's Brochure, informed consent/assent form, parental ICF (for parents/legal guardians), and other relevant documents (as applicable) will be submitted, reviewed, and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol and all substantial changes to the study documentation will require IRB/IEC and regulatory authority review and approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

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 study drug during the study according to the IRB/IEC requirements. The IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor (or designee) before initiation of the study or before an amendment is instituted.

All correspondence with the IRB/IEC and regulatory authorities must be retained within the study regulatory files and made available for inspection.

## 14.2. Informed Consent and Assent

Informed consent and assent from each subject and/or parent/legal guardian must be obtained before any study-specific evaluations are performed. A copy of the signed informed consent (and assent) form will be given to the subject and/or parent/legal guardian; the Investigator will retain the original copies of these documents.

The informed consent/assent 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, as specified in ICH GCP E6 (R2). In the event of an update to the ICF/assent(s), subjects must be re-consented to the most current IRB/IEC-approved version of the ICF/assent(s) prior to continuation of their participation in the study.

## 14.3. Compliance with the Protocol

All processes and procedures defined in this protocol must be adhered to. Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and are deemed by the Investigator as crucial for the safety and well-being of that subject, may be

instituted for that subject only and documented as deviations. The Investigator will contact the Sponsor Medical Monitor as soon as possible regarding such a deviation. These departures do not require pre-approval 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.

## 14.4. Confidentiality

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, with the exception of information that is required by law or regulations to be disclosed to the IRB/IEC, the subject'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 and General Data Protection Regulation) and applicable local/state privacy requirements.

Subjects will be referenced by an assigned subject 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 subject (eg, the signed informed consent/assent 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. In case of any data security breach, the Sponsor will investigate and implement necessary actions.

# 15. STUDY DOCUMENTATION AND GENERAL INFORMATION

## 15.1. General Information

The Investigator should be familiar with and refer, as needed, to the current Investigator's Brochure, along with subsequent Safety Alert Letters, the study-specific Pharmacy Manual, the Laboratory Manual, and all other study-specific information that is provided during the study initiation visit or throughout the duration of the study.

## 15.2. Essential Study Documents

Essential study documents are among the critical documents required before study enrollment is to occur. Essential documents, such as the Investigator's Brochure, study-specific Pharmacy Manual, and final protocol, must be kept onsite in a designated study site file.

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

## 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 and collaborators. At the conclusion of this clinical study, a clinical study report will be prepared. Data generated for this study will be exclusively owned by the Sponsor and collaborators, as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov, ClinicalTrialsRegister.eu, ClinicalTrials.jp, and to any other registries as required by law. After completion of the study, results will be disseminated through the applicable public website(s).

## 15.4. Publication Policy

All unpublished information given to the Investigator by the Sponsor and collaborators shall not be published or disclosed to a third party without the prior written consent of the Sponsor and collaborators.

Policies regarding the publication of the study results are defined in the Clinical Trial Agreement.

## 15.5. Product Handling and Complaints Reporting

If there are any issues during the study related to the quality, packaging, labeling, or characteristics of the study drug, the Investigator, clinical site pharmacist, or pharmacy designee should contact the Sponsor or designated contract research organization as per the Pharmacy Manual within 24 hours of awareness.

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# APPENDIX 1. GUIDANCE ON CONTRACEPTION USE AND PREGNANCY TESTING

Practical guidance on contraception use and pregnancy testing in clinical trials are provided in the following guidance: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

CCI [redacted]

# APPENDIX 3. QUESTIONNAIRES

PROMIS Parent Proxy Mobility, V2.0

PROMIS Parent Proxy Upper Extremity, Short Form 8a, V2.0

CCI [redacted]

PROMIS Pediatric Mobility, V2.0

PROMIS Pediatric Upper Extremity, Short Form 8a, V2.0

CCI [redacted]

CCI [redacted]

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# APPENDIX 4. PROTOCOL VERSION HISTORY

PPD

**Name:** SRP-9001-301-Protocol-V5A4

**Title:** SRP-9001-301-Protocol-V5A4

**Document Number:** PPD

**Type:** Clinical

**SubType:** Protocol Amendment

**Classification:**

**Clinical Study Number:** SRP-9001-301

| Document Approvals | | |
|---|---|---|
| Approval | PPD | |
| Approval | | |
| Approval | | |
| Approval | | |
| Approval | | |
| Approval | | |