CLINICAL STUDY PROTOCOL

DRUG:	SRP-5051
STUDY NUMBER:	5051-102
STUDY TITLE:	An Open-Label Extension Study for Patients with Duchenne Muscular Dystrophy Who Participated in Studies of SRP-5051
IND Number:	CCI
EudraCT Number:	Not applicable
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	Version 5.0 (Amendment 4), 21 April 2020
REPLACES VERSION DATE:	Version 4.0 (Amendment 3), 15 April 2019

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	An Open-Label Extension Study for Patients with Duchenne Muscular Dystrophy Who Participated in Studies of SRP-5051
Study No:	5051-102
Current Version Date:	Version 5.0 (Amendment 4), 21 April 2020

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

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

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

PPD _____ PPD _____

Date (DD-MMM-YYYY)

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

INVESTIGATOR'S AGREEMENT

I have read the Study 5051-102 protocol (Version 5.0 [Amendment 4]) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD-MMM-YYYY)

1. SYNOPSIS

NAME OF COMPANY Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** SRP-5051 Injection **NAME OF ACTIVE INGREDIENT** SRP-5051
TITLE: An Open-Label Extension Study for Patients with Duchenne Muscular Dystrophy Who Participated in Studies of SRP-5051	
Study Number: 5051-102	
Phase of Study: Phase 1/2	
INVESTIGATOR STUDY SITES: This is a multinational clinical trial to be conducted at approximately 100 study sites.	

OBJECTIVES AND CRITERIA FOR EVALUATION:

Primary Objective

- To evaluate the adverse event (AE) profile of repeat every-4-week (Q4W) administration of SRP-5051

Secondary Objectives

- To determine the pharmacokinetics (PK) of SRP-5051 following repeat Q4W administration
- To evaluate additional safety and tolerability of repeat Q4W administration of SRP-5051

CCI [redacted]

Primary Endpoint

- Incidence of AEs

Secondary Endpoints

- Plasma concentrations determined at predose, the maximum observed drug concentration (C_{max}), and 4 to 6 hours after the end of the infusion
- Frequency of clinically relevant abnormalities, as assessed by vital sign measurements, physical examination findings, clinical laboratory tests, and ECGs

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CCI [redacted]

METHODOLOGY:

This is a Phase 1/2 open-label, long-term extension (LTE) study for DMD patients who have completed other studies administering SRP-5051. Each patient will complete 3 periods in this study: Screening, Treatment and Observation, and Safety Follow-up.

Screening Period

Patients who have completed other studies administering SRP-5051 are eligible to participate in this LTE study. For patients who elect to participate in this trial, informed consent is to be obtained at or immediately following the End of Study (EOS) visit in the original study administering SRP-5051. Patients who do not provide consent at the original study's EOS visit will have CCI [redacted] that visit to elect to participate in and provide informed consent for this trial.

Every effort will be made to ensure that patients will not experience any interruption in dosing of SRP-5051 during the transition from the original study administering SRP-5051 to this LTE study.

Treatment and Observation Period

Patients who enroll in this study will receive their first Q4W dose of SRP-5051 on Day 1 of the Treatment and Observation Period.

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While it is expected that patients will receive their Q4W infusions of SRP-5051 at a designated study site (ie, study clinic), home infusions may be an option for dosing visits if circumstances impact a patient's ability to travel by any applicable means (including air travel, personal vehicle travel, car service, wheelchair van, etc.). Prior approval from the Sponsor Medical Monitor is required for any home infusion visit.

Initially, patients will be administered the highest dose determined by a Safety Review Committee (SRC) or Independent Data Monitoring Committee (IDMC) to be safe and tolerable, as justified in other relevant studies of SRP-5051 in accordance with the procedure defined in the relevant study protocol or Charter. The final dose confirmation is to be made by the SRC for this LTE study. The 5051-102 SRC may make the recommendation to proceed to a higher dose level as per the guidance provided in the SRC Charter.

Upon determination of higher dose(s) deemed safe and tolerable in other relevant studies of SRP-5051—and only upon receipt of a formal letter from the Sponsor—dose escalation for all patients enrolled in this LTE study may proceed to the highest dose determined by the 5051-102 SRC to be safe and tolerable, beginning at each patient's next scheduled dosing visit. Data and recommendations from other studies of SRP-5051 will be provided to the 5051-102 SRC to inform the dose-escalation decision.

Patients will continue SRP-5051 dosing Q4W.

Vital sign measurements; physical examination findings; clinical laboratory tests; renal biomarkers; electrocardiograms (ECGs); CCI [redacted] changes in concomitant medications and/or procedures; and AEs will all be assessed during scheduled visits (Table 1).

Clinical laboratory tests will also be collected beginning approximately CCI [redacted] after initial dosing and after each subsequent dose. Refer to the Schedule of Events in Table 1.

CCI [redacted]

Safety Follow-up Period

Clinical laboratory tests, changes in concomitant medications and/or procedures, and AEs will be collected CCI [redacted] after the patient's last dose of SRP-5051.

CCI [redacted] after completing the Treatment and Observation Period, patients will be asked to complete the EOS visit. CCI [redacted] vital sign measurements, physical examination findings, clinical laboratory tests, renal biomarkers, ECGs, changes in concomitant medications and/or procedures, and AEs will be assessed at the EOS visit.

Patients who have received at least 1 dose of study drug and are withdrawn from treatment will be asked to complete an Early Termination visit (to complete the EOS assessments) approximately CCI [redacted] after their last dose of SRP-5051, or within CCI [redacted] of a withdrawal decision if early termination occurs after a missed dose.

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Any AEs are to be recorded through the EOS/Early Termination visit. CCI [redacted]

Patients withdrawn from treatment will not be replaced.

DURATION OF STUDY:

Screening Period: Up to 4 weeks (28 days)

Treatment and Observation Period: Approximately 144 weeks

Safety Follow-up Period: 4 weeks after the last dose

Total duration of patient participation: The maximum duration of each patient's participation in the study is expected to be approximately 152 weeks, inclusive of the Screening, Treatment and Observation, and Safety Follow-up Periods. The maximum study duration will ultimately depend upon patient enrollment from other completed studies of SRP-5051.

NUMBER OF PATIENTS:

The number of patients in this LTE study will be determined by the number of patients who participate in other studies administering SRP-5051.

Up to 60 patients are planned to enroll in this LTE study upon completing a Phase 1 (ie, the completed Study 5051-101) or Phase 2 (eg, the ongoing Study 5051-201) study of SRP-5051 CCI [redacted]

INCLUSION/EXCLUSION CRITERIA:

Note: Patients who do not meet eligibility criteria (ie, screen failures) may be re-screened at the Investigator's discretion.

Inclusion Criteria

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

1. Has completed a study in which SRP-5051 was administered.
2. Has not subsequently received treatment with any investigational therapy for DMD.
3. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose. The sexual partner must also use a medically acceptable form of contraceptive during this period.
4. Is willing to provide informed consent or informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide informed consent for the patient to participate in the study.
5. Is able to understand and comply with all the study requirements and, if under 18 years of age, had as (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.

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Exclusion Criteria

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

1. Initiation or change of dosing (except for modifications to accommodate changes in weight or changes in standard of care) since entering a study administering SRP-5051 for any of the following: angiotensin-converting enzyme inhibitors, angiotensin receptor-blocking agents, β-blockers, and potassium.
2. Requires anti-arrhythmic and/or diuretic therapy for heart failure.
3. Use of any herbal medication/supplement containing aristolochic acid.
4. Treatment with any experimental therapy since entering a study administering SRP-5051, or with any experimental gene therapy for the treatment of DMD at any time.
5. Use of any aminoglycoside antibiotic or statin since entering a study administering SRP-5051.
6. Initiation or change of dosing since completing a study administering SRP-5051 for over-the-counter preparations, such as herbal/nonherbal supplements, vitamins, minerals, and homeopathic preparations.
7. Major surgery since entering a study administering SRP-5051, or planned surgery or procedures that would interfere with the conduct of this study.
8. Presence of other clinically significant illness, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection or malignancy.
9. Any other condition that, in the Investigator's opinion, could interfere with the patient's participation in this trial.
10. Any patient who, in the Investigator's opinion, seems unable/unwilling to comply with the study procedures.
11. Any patient who is taking medications that increase the risk of bleeding in the Investigator's opinion (eg, anticoagulants, antiplatelet agents, novel oral anticoagulants, selective norepinephrine reuptake inhibitors, etc.)

CCI [redacted]

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

SRP-5051 drug product CCI [redacted].

The drug product is supplied for investigational use in single-use, CCI [redacted] glass vials containing CCI [redacted] of the active pharmaceutical ingredient. SRP-5051 drug product is intended CCI [redacted] for intravenous (IV) administration.

Each patient will receive SRP-5051 Q4W for a duration of approximately 144 weeks, at the highest dose determined by an SRC or IDMC to be safe and tolerable in other relevant studies of SRP-5051 and confirmed by the SRC for this LTE study, administered by IV infusion over a period of CCI [redacted].

REFERENCE TREATMENT: None

NAME OF COMPANY	NAME OF FINISHED PRODUCT
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STATISTICAL METHODS:

Sample Size

The study sample size will be determined by the number of patients who participate in other studies administering SRP-5051. Patients are planned to roll over into this LTE study from multiple clinical trials, including trials that are yet to commence.

Analysis Sets

The following analysis sets will be used for the primary and secondary endpoints:

- Safety Set: Defined as all patients who enroll in the study and have started the study drug (SRP-5051) infusion. The dose group will be designated according to the actual dose received. This analysis set will be used for safety analyses.
- PK Set: Defined as all patients who enroll in the study, have started the study drug (SRP-5051) infusion, and have at least 1 PK concentration data collection. This analysis set will be used for PK analyses.

The analysis sets to be used for other endpoints and/or additional analyses will be defined in the statistical analysis plan (SAP).

Statistical Analysis Methods

The following methods will be used for the primary and secondary endpoints:

Safety Analyses

Adverse events and other safety assessments will be summarized descriptively.

PK Analyses

Plasma concentrations at predose, C_{max} (end of infusion), and approximately 4 to 6 hours postdose will be summarized descriptively. Plasma concentration data may be evaluated and combined with other clinical PK data from other studies administering SRP-5051.

CCI [redacted]

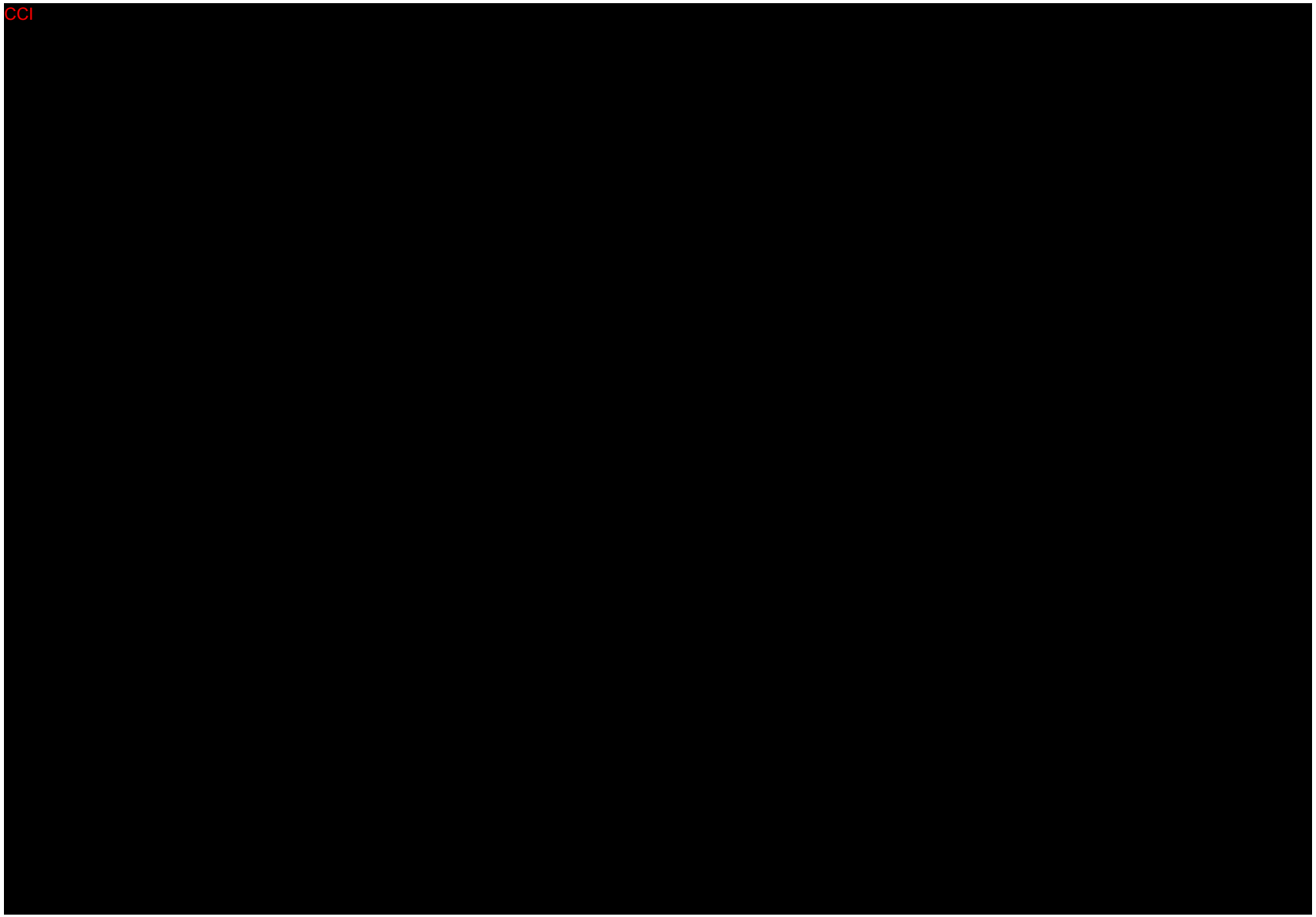
Interim Analysis

No formal interim analysis is planned.

2. SCHEDULE OF EVENTS

The study Schedule of Events is presented in Table 1.


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

TABLE OF CONTENTS

CCI

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LIST OF TABLES

LIST OF FIGURES

CCI

[redacted]

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CCI	CCI
CCI	CCI
ACE	Angiotensin-converting enzyme
ADL	Activities of daily living
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of special interest
aHUS	Atypical hemolytic uremic syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin receptor-blocking
AST	Aspartate aminotransferase
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
CCI	CCI
BW	Body weight
CK	Creatine kinase
C_{max}	Maximum observed plasma concentration
CPP	Cell-penetrating peptide
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMD	Duchenne muscular dystrophy
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
CCI	CCI
FVC	Forced vital capacity
GCP	Good Clinical Practice

Abbreviation	Definition
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
HPF	High-power field
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous(ly)
IVAD	Implanted venous access device
LTE	Long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
CCI	CCI
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NHP	Nonhuman primate
NOAEL	No-observed-adverse-effect level
CCI	CCI
OECD	Organisation for Economic Co-operation and Development
CCI	CCI
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
CCI	CCI

Abbreviation	Definition
PMO	Phosphorodiamidate morpholino oligomer
PPMO	Peptide-conjugated phosphorodiamidate morpholino oligomer
PT	Preferred term
CCI	CCI [redacted]
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
CCI	CCI [redacted]
QUA	Quantitative urinalysis
QW	Once weekly
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
SWFI	Sterile water for injection
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
UACR	Urinary albumin to creatinine ratio
ULN	Upper limit of normal
UPCR	Urinary protein to creatinine ratio
WHODrug	World Health Organization Drug Dictionary
WNL	Within normal limits

Note: Abbreviations that only appear in a table or figure are defined within the footer of the corresponding table or figure.

5. INTRODUCTION

5.1. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare, serious, life-threatening, X-linked recessive, degenerative neuromuscular disease caused by mutations in the dystrophin gene, with a worldwide incidence of 1 in 3500 to 5000 newborn boys, irrespective of geographical region, race, or population density (Centers for Disease Control and Prevention 2009, Emery 1991). The mutations that cause DMD typically disrupt the dystrophin messenger ribonucleic acid (mRNA) reading frame and prevent production of the corresponding protein. Dystrophin is a critically important part of a 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 contraction causes widespread, chronic, and progressive muscle damage and degeneration, with replacement by fat and fibrotic tissue. The clinical effect of this disrupted dystrophin reading frame is ultimately fatal.

The progression of DMD follows a highly predictable disease course. Significant motor deficits may be present during the first year of life, but a diagnosis is usually made between the ages of 3 to 5 years, when children begin to show functional symptoms (eg, waddling gait, toe walking, and difficulty climbing stairs). Over time, ambulation becomes increasingly abnormal, and by 8 years of age, most patients have lost the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking. By 10 to 14 years of age, most patients are wheelchair-dependent. Weakness of the arms and increasingly limited upper-limb function, contractures, decubitus ulcers, and scoliosis (which often requires surgery) occur frequently (Brooke 1989). While pulmonary and cardiac function are generally normal during early childhood, the cardiac and diaphragmatic muscles of DMD patients progressively weaken during late childhood and adolescence, leading to eventual dependence on ventilatory support (Brooke 1989, Eagle 2002).

In addition to clinical manifestations, patients with DMD have greatly elevated creatine kinase (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) (normal range: 37 U/L to 430 U/L), 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 DMD patients (McMillan 2011). Creatinine levels tend to be low or low to normal due to decreased muscle mass (Viollet 2009).

Existing interventions are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation.

Current pharmacologic treatments, such as corticosteroids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function (Beenakker 2005, Pradhan 2006).

However, their benefits are only temporary, and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, Cushingoid facies and habitus, and cataracts (Biggar 2006, Manzur 2008).

5.2. Phosphorodiamidate Morpholino Oligomers and Peptide-Conjugated Phosphorodiamidate Morpholino Oligomers

5.2.1. Phosphorodiamidate Morpholino Oligomers

Antisense ribonucleic acid (RNA) therapeutics are a class of compounds composed of heterocyclic nucleobases (adenine, cytosine, guanine, and thymine, or analogues) linked together on an oligomer backbone that are designed to hybridize with specific complementary RNA targets via Watson-Crick base pairing. Ribonucleic acid therapeutics can be synthesized to bind targeted RNA sequences in a pathogen or pathogenic process to treat a wide range of diseases through positively or negatively modulating gene expression. Additionally, RNA therapeutics can be synthesized to target a pre-mRNA in the nucleus of a cell to influence the splicing process that creates a mature mRNA. Referred to as “exon skipping”, this approach allows determination of which exons will be incorporated into the mature mRNA to be translated into the protein product.

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

5.2.2. Peptide-Conjugated Phosphorodiamidate Morpholino Oligomers

5.2.2.1. SRP-5051

The peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) SRP-5051 is composed of 2 covalently bonded moieties, corresponding to the classical pharmacology concept of “message and address.”

The first moiety is a PMO designed to hybridize to an internal nucleobase sequence of exon 51 in the dystrophin gene pre-mRNA to induce the skipping of exon 51 in the mature mRNA, thereby restoring the disrupted open reading frame caused by deletion mutations of the dystrophin gene, which in turn leads to the production of an internally shortened dystrophin protein. The second moiety is a cell-penetrating peptide (CPP) that greatly enhances intracellular delivery of PMOs in general via the mechanism of fluid-phase endocytosis.

5.3. Nonclinical Experience with SRP-5051

Nonclinical studies of SRP-5051 conducted to date are summarized below. Refer to the SRP-5051 Investigator's Brochure for additional details of each study.

5.3.1. Nonclinical Summary

Clinical development of SRP-5051 is supported by nonclinical evaluation of in vitro absorption, distribution, metabolism, and excretion (ADME) studies, nonclinical safety pharmacology studies, and nonclinical toxicity/toxicokinetic studies of SRP-5051 conducted in [redacted] animal species: the mouse, nonhuman primate (NHP)[redacted].

All safety pharmacology and toxicity studies of SRP-5051 considered necessary for human safety assessment were conducted in accordance with the Organization for Economic Co-operation and Development (OECD) Test Guidelines and Principles of Good Laboratory Practice (GLP) in countries (United States, Canada) that are members of the OECD Mutual Acceptance of Data program.

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

5.4. Clinical Experience with SRP-5051

Clinical experience with SRP-5051 to date is summarized below. Refer to the SRP-5051 Investigator's Brochure for additional details of each clinical study.

5.4.1. Completed Studies of SRP-5051

One study of SRP-5051 (Study 5051-101) has been completed to date, as summarized below in Section 5.4.1.1.

5.4.1.1. Study 5051-101 (Phase 1 Single-Ascending-Dose Study in DMD Patients)

The completed Study 5051-101 was a Phase 1, first-in-human, open-label trial to evaluate the safety, tolerability, and PK of a single dose of SRP-5051—CCI [redacted]—in patients with DMD amenable to exon 51-skipping treatment.

A total of [redacted] patients were enrolled and dosed in Study 5051-101 [redacted]

[redacted]

[redacted]

[redacted]

5.4.2. Ongoing Studies of SRP-5051

In addition to this long-term extension (LTE) study, 2 other studies of SRP-5051 remain ongoing to date, as summarized below in Sections 5.4.2.1 and 5.4.2.2.

5.4.2.1. Study 5051-103 (Phase 1 Single-Ascending-Dose Study in Healthy Male Subjects)

Study 5051-103 is an open-label, single-center study conducted in healthy male subjects. The primary objective of the study is to evaluate the safety and tolerability [redacted] of SRP-5051 [redacted] administered as an IV infusion in healthy subjects. The secondary objective is to determine the PK of the [redacted] doses in this population.

5.4.2.2. Study 5051-201 (Phase 2, Two-Part, Multiple-Ascending-Dose Study in DMD Patients)

Study 5051-201 is a multicenter, open-label study conducted in DMD patients amenable to exon 51 skipping. The study comprises 2 parts: Part A, which is primarily intended to evaluate the safety and tolerability of SRP-5051 at multiple ascending dose levels (4 mg/kg [n = 3], 10 mg/kg [n = 3], 20 mg/kg [n = 3], 30 mg/kg [n = 6], and 40 mg/kg [n = 6]) and determine the MTD, and Part B, which is primarily intended to evaluate dystrophin protein levels after treatment with SRP-5051 at the MTD and which includes an expansion cohort (n = ~15).

5.5. Rationale for the Current Study

This LTE study is intended for DMD patients who have completed other studies administering SRP-5051. The trial is being conducted to offer participants who have received SRP-5051 in other trials the opportunity to continue dosing with SRP-5051. The trial is also intended to gain additional insight into the safety and efficacy of treatment with SRP-5051 and the potential possibility for patients to experience clinical benefit.

Current data from completed chronic toxicology studies in mice and NHPs CCI [redacted] offer a reasonable assurance of minimal risk for Q4W administration of SRP-5051.

Data from other clinical studies of SRP-5051, CCI [redacted] are anticipated to further inform the continued conduct of this study.

5.6. Benefit and Risk Assessment

The clinical benefit of SRP-5051 for the treatment of DMD patients is currently under evaluation, but is not yet known. However, in nonclinical studies, PD proof of concept for the dose-dependent exon 51-skipping activity of SRP-5051 has been demonstrated in various preparations of skeletal muscle obtained from DMD patients in vitro; in transgenic mice harboring the complete human *DMD* gene; and in skeletal and cardiac muscle following single-dose, CCI [redacted] IV administration of SRP-5051 in studies conducted in healthy NHPs in vivo. Pharmacokinetic/PD analyses support an anticipated pharmacodynamically relevant response at selected doses of SRP-5051, administered Q4W, in both healthy human subjects and DMD patients.

Additional supportive data for the PD mechanism of action and enhanced delivery of SRP-5051 are provided by studies of a murine surrogate PMO, AVI-4225, which causes exon 23 skipping in pre-mRNA in a murine DMD model (*mdx* mouse) in vivo (refer to the current SRP-5051 Investigator's Brochure for details). The observed levels of exon skipping and dystrophin protein (as assessed in a quantitative Western blot assay) with the CPP-conjugated AVI-4225 were superior to those observed with unconjugated AVI-4225 at equivalent doses. Specifically, dystrophin levels were > 10-fold higher after CPP-conjugated AVI-4225 treatment compared to unconjugated AVI-4225 treatment. In the *mdx* mouse, exon-skipping levels were observed to persist for up to 3 months after a single dose of CPP-conjugated AVI-4225.

These results provide strong evidence to support both the proposed mechanism of action of exon skipping and the desired pharmacological effect on dystrophin protein content. Therefore, it is possible that treatment with SRP-5051 may confer benefit via production of dystrophin, which may ultimately lead to positive clinical effects on muscle function in DMD patients amenable to exon 51 skipping.

In nonclinical safety studies of SRP-5051, no evidence of central nervous system effects, genotoxicity, male reproductive toxicity, or immune responses was detected.

Cardiovascular findings were limited [redacted]

As of 29 November 2019, the SRP-5051 clinical development program consisted of 4 clinical trials, including 2 Phase 1 studies (the completed Study 5051-101 and ongoing Study 5051-103); this Phase 1/2 LTE study; and 1 Phase 2 study (the ongoing Study 5051-201).

As reported in the SRP-5051 Investigator's Brochure, [redacted] SAEs—[redacted] reported as of the 29 November 2019 data cutoff date, and [redacted] reported subsequent to that data cutoff—were reported in a total of [redacted] clinical study participants receiving SRP-5051. All of these SAEs were assessed as not related to SRP-5051 by both the Sponsor and the reporting Investigators. No new safety trends were detected in the distribution of the SAEs, cumulatively. There were no fatal cases reported from the clinical development program.

Overall, these safety data suggest that that SRP-5051 has an acceptable safety profile in DMD patients. Information about important risks, potential risks, and other risks associated with SRP-5051 treatment, as well as details of the AEs reported in clinical study participants receiving SRP-5051, are provided in the SRP-5051 Investigator's Brochure.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

- To evaluate the AE profile of repeat Q4W administration of SRP-5051

6.1.2. Secondary Objectives

- To determine the PK of SRP-5051 following repeat Q4W administration
- To evaluate additional safety and tolerability of repeat Q4W administration of SRP-5051

CCI [redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

- Incidence of AEs

6.2.2. Secondary Endpoints

- Plasma concentrations determined at predose, the maximum observed drug concentration (C_{max}), and 4 to 6 hours after the end of the infusion
- Frequency of clinically relevant abnormalities, as assessed by vital sign measurements, physical examination findings, clinical laboratory tests, and ECGs

CCI [redacted]


CCI

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 1/2, multicenter, open-label, LTE study for patients who have completed other studies administering SRP-5051. The study will assess the safety, tolerability, and PK of SRP-5051 administered Q4W for a duration of approximately 144 weeks in patients with DMD who have deletion mutations amenable to exon 51-skipping treatment.

Up to 60 patients are planned to enroll in this LTE study upon completing a Phase 1 (ie, the completed Study 5051-101 [Section 5.4.2.1]) or Phase 2 (eg, the ongoing Study 5051-201 [Section 5.4.2.2]) study of SRP-5051 CCI [redacted].

Each patient will complete 3 study periods: Screening, Treatment and Observation, and Safety Follow-up. Details are as follows:

Screening Period

Patients who have completed other studies administering SRP-5051 are eligible to participate in this LTE study. For patients who elect to participate in this trial, informed consent is to be obtained at or immediately following the End of Study (EOS) visit in the original study administering SRP-5051. Patients who do not provide consent at the original study EOS visit will have CCI [redacted] the time of that visit to elect to participate in and provide informed consent for this trial. Every effort will be made to ensure that the patient will not experience any interruption in dosing of SRP-5051 during the transition from the original study to this LTE study.

Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen-failure details, eligibility criteria, and any SAE information.

Individuals who do not meet the criteria for participation in this study (ie, screen failures) may be re-screened at the Investigator's discretion.

Treatment and Observation Period

Patients who enroll in this study will receive their first Q4W dose of SRP-5051 on Day 1 of the Treatment and Observation Period. While it is expected that patients will receive their Q4W infusions of SRP-5051 at a designated study site (ie, study clinic), home infusions may be an option for dosing visits if circumstances impact a patient's ability to travel by any applicable means (including air travel, personal vehicle travel, travel via car service, wheelchair van travel, etc.). Prior approval from the Sponsor Medical Monitor is required for any home infusion visit.

Initially, patients will be administered the highest dose determined by a Safety Review Committee (SRC) or Independent Data Monitoring Committee (IDMC) to be safe and tolerable, as justified in other relevant studies of SRP-5051 in accordance with the procedure defined in the relevant study protocol or Charter, with the final dose confirmation to be made by the SRC for this LTE study.

The SRC for this LTE study (Section 7.5.1) may make the recommendation to proceed to a higher dose level as per the guidance provided in the SRC Charter.

Upon determination of higher dose(s) deemed safe and tolerable in other relevant studies of SRP-5051—and only upon receipt of a formal letter from the Sponsor—dose escalation for all patients enrolled in this LTE study may proceed to the highest dose determined by the 5051-102 SRC to be safe and tolerable, starting at each patient's next scheduled dosing visit (Table 1). Data and recommendations from other studies of SRP-5051 will be provided to the 5051-102 SRC to inform the dose-escalation decision.

Patients will continue SRP-5051 dosing Q4W. Vital sign measurements; physical examination findings; clinical laboratory tests; renal biomarkers; electrocardiograms (ECGs); CCI [redacted] changes in concomitant medications and/or procedures; and AEs will all be assessed during scheduled visits (Table 1).

Vital signs will be collected from the contralateral arm from which the blood samples are collected. Clinical laboratory tests will also be collected, approximately CCI after initial dosing and after each subsequent dose, for safety monitoring purposes. Refer to Section 9.3 for safety monitoring guidance. These laboratory assessments may be collected at the patient's home or another convenient location, but must be analyzed centrally.

Safety Follow-up Period

Patients will be contacted by the clinic staff CCI after their last dose of SRP-5051 to assess AEs and changes in concomitant medications and/or procedures. Clinical laboratory tests will be collected at this time at the study site or another convenient location, and analyzed centrally.

CCI after completing the Treatment and Observation Period, patients will be asked to complete the EOS visit. CCI vital sign measurements, physical examination findings, clinical laboratory tests, renal biomarkers, ECGs, changes in concomitant medications and/or procedures, and AEs will be assessed at the EOS visit.

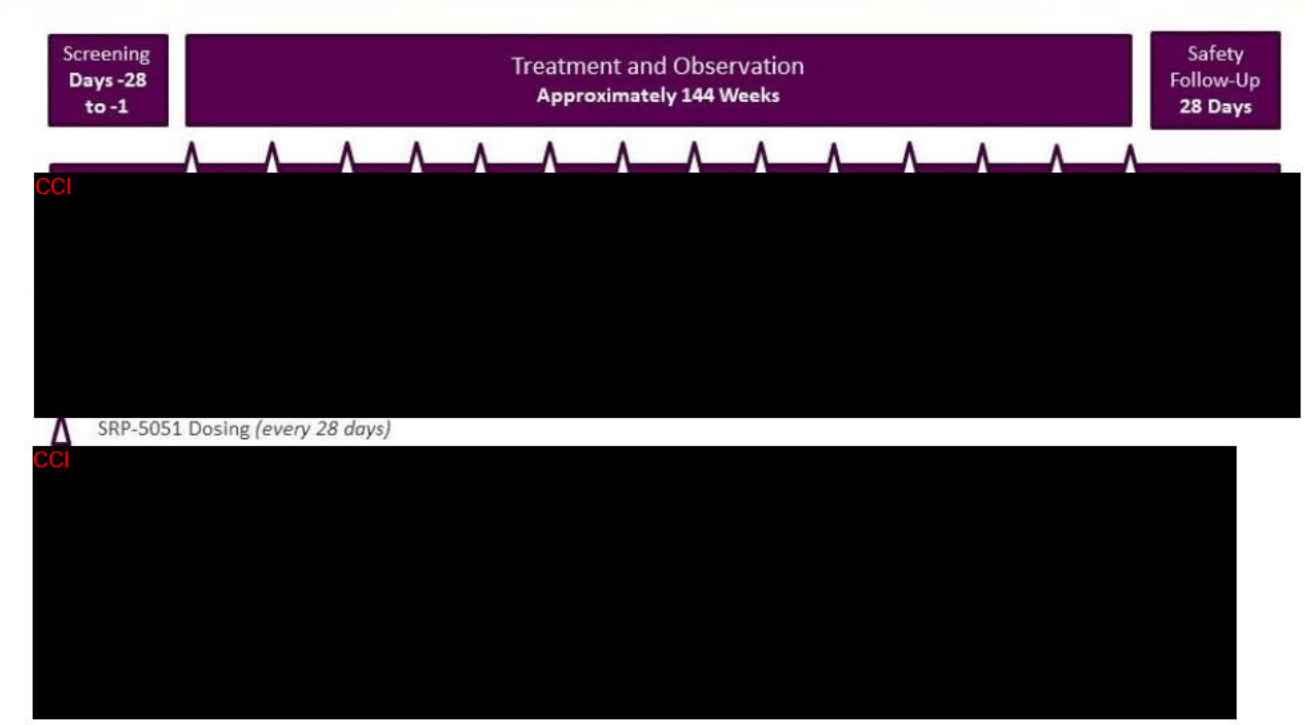
Patients who have received at least 1 dose of study drug and are withdrawn from treatment will be asked to complete an Early Termination visit (to complete the EOS assessments) approximately CCI after their last dose of SRP-5051, or within CCI of a withdrawal decision if early termination occurs after a missed dose.

Any AEs are to be recorded through the EOS/Early Termination visit. CCI [redacted]

Patients withdrawn from treatment will not be replaced.

A schematic of the study design is presented in Figure 1. The study Schedule of Events is provided in Table 1.

Figure 1: Study Design Schematic



EOS = End of Study; ET = Early Termination; SCR = Screening.

7.2. Dose Selection Rationale

Completed nonclinical studies in mice, NHPs, CCI [redacted] support Q4W IV dosing of SRP-5051 in the clinical setting (Section 5.3).

The starting dose of SRP-5051 in this study will be the highest dose determined by an SRC or IDMC to be safe and tolerable, as justified in other relevant studies of SRP-5051 in accordance with the procedure defined in the relevant study protocol or Charter, with the final dose confirmation to be made by the SRC for this LTE study.

7.3. Stopping Rules

Stopping rules for this study are detailed below in Sections 7.3.1 through 7.3.5.

7.3.1. Stopping Rules for Liver Test Results

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor**, dosing of a patient with SRP-5051 will be stopped permanently; values that are not confirmed due to failure to retest or missing laboratory values will be presumed confirmed:

- Gamma glutamyl transferase (GGT) or glutamate dehydrogenase (GLDH) CCI × ULN, which is confirmed
- GGT or GLDH CCI × ULN, which is confirmed and persists for CCI
- GGT or GLDH CCI × ULN, which is confirmed, **and** total bilirubin CCI × ULN or international normalized ratio (INR) CCI
- GGT or GLDH CCI × ULN, which is confirmed, and new appearance (ie, onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, or eosinophilia CCI considered by the Investigator to be potentially related to hepatic inflammation

7.3.2. Stopping Rules for Renal Test Results

CCI [redacted]

CCI [redacted]

7.3.3. Stopping Rules for Hypersensitivity Adverse Events

In the event of a confirmed hypersensitivity AE meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor**, dosing of a patient with SRP-5051 will be stopped permanently:

- Anaphylaxis, anaphylactoid reaction, or angioedema
- Any serious allergic reaction
- Any serious, acute complement-mediated reaction (eg, atypical hemolytic uremic syndrome [aHUS], acute kidney injury, arteritis, myocarditis, pneumonitis, etc.)

7.3.4. Stopping Rules for Platelet Count Results

In the event of laboratory results meeting the following criteria**, and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor**, dosing of a patient with SRP-5051 will be stopped permanently:

- Platelet count CCI [redacted]

7.3.5. Stopping Rules Are Not Applicable for Rhabdomyolysis

Stopping rules are not applicable for rhabdomyolysis. In the event of a rhabdomyolysis AE, safety monitoring is to be implemented as instructed in Section 9.3.5. Dose interruption/delay may occur, as described in Section 9.2.2.1.

7.4. Trial Discontinuation

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

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

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC, or regulatory authority
- Insufficient adherence to protocol requirements consistent with the European Clinical Trial Directive 2005/28/EC

7.5. Study Committees

7.5.1. Safety Review Committee

The SRC for this study will evaluate the study safety and tolerability data on an ongoing basis in order to ensure that the patients are not exposed to unreasonable or unnecessary risks.

The SRC may also make the recommendation to proceed to a higher dose level as per the guidance provided in the SRC Charter. Upon determination of higher dose(s) deemed safe and tolerable in other relevant studies of SRP-5051—and only upon receipt of a formal letter from the Sponsor—dose escalation for all patients enrolled in this LTE study may proceed to the highest dose determined by the 5051-102 SRC to be safe and tolerable, starting at each patient's next scheduled dosing visit (Table 1). Data and recommendations from other studies of SRP-5051 will be provided to the 5051-102 SRC to inform the dose-escalation decision.

The activities and composition of the SRC are further detailed in the SRC Charter, which was ratified during the initial SRC meeting prior to the commencement of dosing of patients. The SRC Charter contains guidance for evaluation of available safety data and additional safety monitoring for toxicities.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Number of Patients

The number of patients in this study will be determined by the number of patients who participate in other studies administering SRP-5051.

Up to 60 patients with DMD who have completed a Phase 1 (ie, the completed Study 5051-101 [Section 5.4.1.1]) or Phase 2 study (eg, the ongoing Study 5051-201 [Section 5.4.2.2]) of SRP-5051 CCI [redacted].

8.2. Patient Inclusion Criteria

Note: Patients who do not meet eligibility criteria may be re-screened at the Investigator's discretion.

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

I 1. Has completed a study in which SRP-5051 was administered.

I 2. Has not subsequently received treatment with any investigational therapy for DMD.

I 3. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose. The sexual partner must also use a medically acceptable form of contraceptive during this time frame.

I 4. Is willing to provide informed consent or informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide informed consent for the patient to participate in the study.

I 5. Is able to understand and comply with all the study requirements and, if under 18 years of age, had as (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.

8.3. Patient Exclusion Criteria

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

E 1. Initiation or change of dosing (except for modifications to accommodate changes in weight or changes in standard of care) since entering a study administering SRP-5051 for any of the following: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor-blocking (ARB) agents, β-blockers, and potassium.

E 2. Requires anti-arrhythmic and/or diuretic therapy for heart failure.

E 3. Use of any herbal medication/supplement containing aristolochic acid.

E 4. Treatment with any experimental therapy since entering a study administering SRP-5051, or with any experimental gene therapy for the treatment of DMD at any time.

E 5. Use of any aminoglycoside antibiotic or statin since entering a study administering SRP-5051.

E 6. Initiation or change of dosing since completing a study administering SRP-5051 for over-the-counter preparations, such as herbal/nonherbal supplements, vitamins, minerals, and homeopathic preparations.

E 7. Major surgery since entering a study administering SRP-5051, or planned surgery or procedures that would interfere with the conduct of this study.

E 8. Presence of other clinically significant illness, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection or malignancy.

E 9. Any other condition that, in the Investigator's opinion, could interfere with the patient's participation in this trial.

E 10. Any patient who, in the Investigator's opinion, seems unable/unwilling to comply with the study procedures.

E 11. Any patient who is taking medications that increase the risk of bleeding in the Investigator's opinion (eg, anticoagulants, antiplatelet agents, novel oral anticoagulants, selective norepinephrine reuptake inhibitors, etc.)

CCI [redacted]

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

A patient will be considered to have completed the study upon completion of the Safety Follow-up assessments as specified in the Schedule of Events (Table 1).

8.5. Completion of the Trial

The trial will be considered completed when all patients have completed the Safety Follow-up assessments as specified in the Schedule of Events (Table 1). The study duration will be contingent on enrollment.

8.6. Patient Withdrawal Criteria

Any patient can decide to withdraw from study participation at any time for any reason. In addition, the study Sponsor may decide to stop the study participation of any patient as deemed necessary. The Investigator may also stop the study participation of any patient at any time. Reasons for withdrawal from the study include, but are not limited to:

- The patient was erroneously included in the study (ie, was found to not have met the eligibility criteria)
- The patient experiences an intolerable or unacceptable AE
- The patient is unable to comply with the requirements of the protocol

- Laboratory results during monitoring meet protocol-defined criteria for dosing discontinuation (refer to Section 9.3 for guidance on safety monitoring and dosing decisions and to Section 7.3 for the study stopping rules)

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

Patients who have received at least 1 dose of study drug and are withdrawn from treatment will be asked to complete an Early Termination visit (to complete the EOS assessments) approximately CCI after their last dose of SRP-5051, or within CCI of a withdrawal decision if early termination occurs after a missed dose. Any AEs are to be recorded through the EOS/Early Termination visit. CCI

Patients withdrawn from treatment will not be replaced.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

SRP-5051 drug product is a CCI [redacted]. SRP-5051 drug product is supplied for investigational use in CCI [redacted] of the active pharmaceutical ingredient.

The SRP-5051 drug product is intended for reconstitution with CCI [redacted] of sterile water for injection (SWFI), followed by dilution with CCI [redacted] for IV administration. The diluents for reconstitution or preparation of the dosing solution are not supplied with the drug product. The SRP-5051 drug product will be supplied CCI [redacted]

Details of the study drug are summarized in Table 2. Refer to the study-specific Pharmacy Manual for further information on packaging, labeling, and preparation instructions.

Table 2: Study Drug Specifications

Study drug name:	SRP-5051 injection
Strength:	CCI [redacted]/vial
Dosage formulation:	CCI [redacted] **NOTE: The drug product must initially be reconstituted with CCI [redacted] of sterile water for injection and additionally diluted to the appropriate dose and volume in CCI [redacted] prior to administration.**
Dosage:	Initial dose will be the highest dose determined by a Safety Review Committee (SRC) or Independent Data Monitoring Committee to be safe and tolerable, as justified in other relevant studies of SRP-5051, with the final dose confirmation to be made by the SRC for this long-term extension study.
Route of administration:	Intravenous infusion, after reconstitution and dilution
Dosing instructions:	Infused over CCI [redacted]
Packaging and labeling:	SRP-5051 is supplied in single-use vials containing CCI [redacted] of SRP-5051. Each vial is labeled in accordance with applicable laws and regulations.

9.1.1. Packaging and Labeling

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

The label text for the study drug product will include the following information: product name/identifier, cautionary statement, lot number (or alternative code), storage conditions, and the name of the study Sponsor. Additional information may be included in accordance with applicable local, national, or regional requirements.

9.1.2. Storage

The study drug product must be stored CCI [redacted]. Vials of investigational product (IP) must be stored in a secured, limited access area with appropriate temperature recording, controls, and monitoring. Details for storage can be found in the study-specific Pharmacy Manual.

9.2. Treatment Administered

Eligible patients will receive an IV infusion of SRP-5051 Q4W for approximately 144 weeks. While it is expected that patients will receive their Q4W infusions of SRP-5051 at a designated study site (ie, study clinic), home infusions may be an option for dosing visits if circumstances impact a patient's ability to travel by any means. Prior approval from the Sponsor Medical Monitor is required for any home infusion visit.

SRP-5051 is to be prepared for dosing by following the steps detailed in the study-specific Pharmacy Manual.

Each patient will receive SRP-5051 by IV infusion over a period of CCI [redacted]. The Q4W dose of SRP-5051 will not exceed the highest dose determined by an SRC or IDMC to be safe and tolerable in other relevant studies of SRP-5051, with the final dose confirmation to be made by the SRC for this LTE study.

SRP-5051 is to be administered through a peripheral IV. If peripheral access cannot be obtained, alternative methods of obtaining IV access must be attempted. An implanted venous access device (IVAD) is only to be considered, at the discretion of the Investigator, if alternative options have been attempted and access continues to be unsuccessful.

If SRP-5051 is administered into an existing IV line, the line is to be flushed with normal saline before and after administration of SRP-5051. After SRP-5051 administration and the saline flush, the IVAD may be flushed with heparin in order to hep-lock the device prior to removal of the infusion line.

No other medications may be administered concomitantly during the study drug infusion.

All patients will be observed for at least CCI [redacted] following the end of the infusion of study drug. In the absence of either a) infusion-related reactions (IRRs) (whether local or systemic) or b) other symptoms or signs of hypersensitivity associated with drug administration following CCI [redacted] consecutive SRP-5051 administrations at the same dose level, monitoring beyond CCI [redacted] post-end of infusion is not required.

9.2.1. Dose Modification Criteria

Patient-level dose modification guidance for this LTE study is provided below.

Refer to Section 7.2.1 (dose escalation) and Section 7.3 (stopping rules) for study-level dose-modification information.

9.2.2. Dose Interruption Criteria

If a patient in this study experiences an AE that requires interruption of administration of study drug for CCI consecutive doses, the Investigator is to consult with the Medical Monitor to determine whether the patient may resume treatment.

9.2.2.1. Dose Interruption/Delay Due to Laboratory Parameters Meeting Relevant Criteria

If a patient has a scheduled dosing visit, but SRP-5051 administration is held due to laboratory parameters meeting relevant criteria (Section 9.3)—including any of the AEs of special interest (AESIs) defined in Section 11.1.3— the following study procedures are to be performed as scheduled (Table 1):

- Safety laboratory assessments
- Physical examination
- Weight measurement
- 12-lead ECG
- Vital sign measurements
- Concomitant medication and procedure monitoring
- AE monitoring
- Physiotherapeutic intervention(s)

CCI

If repeat laboratory assessment results are within the allowable thresholds, and the patient has an unscheduled visit for SRP-5051 dosing within the designated CCI window, the following study procedures are to be performed as scheduled (Table 1):

- Urine dipstick
- QUA
- Serum cystatin C assessment
- Weight measurement
- Vital sign measurements

CCI

- Plasma PK sampling (if applicable for the visit)

If SRP-5051 dosing is postponed due to laboratory abnormalities, the dose may subsequently be administered outside the CCI window specified in the Schedule of Events (Table 1), provided that:

- Repeat laboratory test results are within the allowable thresholds as per Section 9.3, **and**
- No CCI doses of SRP-5051 CCI are administered within 14 days.

9.3. Safety Monitoring

9.3.1. Safety Monitoring for Liver Chemistry Tests

Liver chemistry tests are to be monitored as specified in the Schedule of Events (Table 1). Initial abnormal liver chemistry test result(s) are to be confirmed if:

- GGT or GLDH or AST or ALT measurement is CCI × ULN (or CCI × Baseline value, if the Baseline value was CCI ULN) at any time during the study

Patients with confirmed abnormal liver chemistry test results (as detailed immediately above) must have their liver chemistry (GGT, GLDH, ALT, AST, alkaline phosphatase [ALP], INR, and total bilirubin) retested CCI . CCI if abnormalities stabilize, or if the study drug has been discontinued and the patient is asymptomatic.

Stopping rules for liver chemistry test results are provided in Section 7.3.1.

9.3.1.1. Additional Investigations for Liver Function

For patients with confirmed abnormal liver chemistry test results (as detailed above in Section 9.3.1), it is recommended that the following additional evaluations be performed:

CCI

9.3.2. Safety Monitoring for Renal Function

Renal tests are to be monitored as specified in the Schedule of Events (Table 1) and the renal monitoring decision trees provided in Figure 2 (local analysis) and Figure 3 (central analysis).

Patients with the following test results must undergo repeat testing for confirmation of the abnormal results:

- Protein [redacted] (dipstick)
- Urinary protein to creatinine ratio (UPCR) [redacted] or [redacted]
- Urinary albumin to creatinine ratio (UACR) [redacted] or [redacted]
- Serum creatinine [redacted] above Baseline or [redacted] above Baseline
- Serum creatinine [redacted] × ULN
- Estimated glomerular filtration rate (eGFR) [redacted]
- RBCs [redacted]/HPF
- Elevated serum cystatin C > ULN

Stopping rules for renal test results are provided in Section 7.3.2.

9.3.2.1. Additional Investigations for Renal Function

[redacted] urine collection is to be undertaken to quantify any proteinuria and GFR changes indicated by confirmed abnormal test results, as detailed above in Section 9.3.2.

Additional evaluations—including nephrology consultation, renal ultrasound/CT/MRI, and renal biopsy—may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.


CCI

CCI

[redacted]

9.3.3. Safety Monitoring for Hypersensitivity

Patients will be monitored for the occurrence of allergic reactions or complement-mediated reactions primarily via monitoring of AEs, as specified in the Schedule of Events (Table 1). Patients will be instructed to promptly report any signs or symptoms of fever or constitutional symptoms that may arise during the study, and the Investigator must closely evaluate all potential causes, including concomitant illness. In addition to monitoring of AEs, routine laboratory monitoring for complement-mediated reactions CCI [redacted] will be performed as outlined in the Schedule of Events (Table 1).

Stopping rules for hypersensitivity AEs are provided in Section 7.3.3.

9.3.3.1. Additional Investigations for Hypersensitivity

Patients who experience significant or persistent constitutional symptoms (as detailed above in Section 9.3.3) are to discuss these symptoms with the Sponsor 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 Sponsor Medical Monitor.

9.3.4. Safety Monitoring for Platelet Count Results

Platelet count is to be monitored as specified in the Schedule of Events (Table 1).

Patients who have a confirmed occurrence of platelets CCI [redacted] must have the following evaluations performed:

CCI [redacted]

Stopping rules for platelet count results are provided in Section 7.3.4.

9.3.4.1. Additional Investigations for Platelet Count

Additional platelet evaluations for confirmed, unexplained, and significant platelet count reductions (as detailed above in Section 9.3.4)—including CCI [redacted] —may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.

9.3.5. Safety Monitoring for Rhabdomyolysis

Monitoring for rhabdomyolysis must occur through urine dipstick and monitoring of AEs, as specified in the Schedule of Events (Table 1).

Patients with confirmed heme+ dipstick urinalysis are to be evaluated for urine microscopy and for the following AEs:

- Rhabdomyolysis
- Acute onset or exacerbation of myalgia
- Myoglobinuria
- Chromaturia (eg, tea-colored urine)

There are no applicable stopping rules for rhabdomyolysis.

9.3.5.1. Additional Investigations for Rhabdomyolysis

In the event of any of the AEs detailed above in Section 9.3.5, patients must undergo evaluations of myoglobinuria, CK, renal function (eg, serum cystatin C), and serum chemistry CCI [redacted] until values reach usual/pre-event levels or stabilize.

In addition, Investigators are to obtain a more detailed history of symptoms, preceding activity and hydration status, concomitant drug use, and recent or concurrent infection(s).

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

9.4. Randomization and Blinding

This study is open-label. No randomization will be performed. Neither the patient, the patient's parent(s)/caregiver(s), nor study personnel will be blinded to study drug.

9.5. Prior and Concomitant Medications

No other medications may be administered concomitantly during the infusion of SRP-5051.

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

- Treatment with any other exon-skipping therapy or any experimental gene therapy for the treatment of DMD.
- Immunosuppressants (other than oral or systemic corticosteroids)
- Systemic aminoglycoside antibiotic or statin
- Since entering a study administering SRP-5051, initiation or change of dosing (except for modification to accommodate changes in weight or changes in standard of care) for ACE inhibitors, ARB agents, β-blockers, potassium, herbal/nonherbal supplements, vitamins, minerals, or homeopathic preparations.

- Medications that can increase the risk of bleeding in the Investigator's opinion (eg, anticoagulants, antiplatelet agents, novel oral anticoagulants, selective norepinephrine reuptake inhibitors, etc.).
- Anti-arrhythmic therapies, diuretics, and any herbal medication/supplement containing aristolochic acid are prohibited during the trial.

The dosage of any medication should be constant for at least 4 weeks prior to Day 1 and throughout the study, unless clinically indicated.

The Investigator is to contact the Medical Monitor if he/she is unsure about changing a specific medication, or is uncertain if an herbal medicine/supplement contains aristolochic acid.

Any medication taken by a patient during the course of the study, the reason for its use (ie, indication), and any modification to the dose of that medication and the reason for the modification (ie, corresponding indication) will be documented in the source documents and the electronic case report form (eCRF).

9.6. Treatment Compliance

All doses will be administered under the direct supervision of trained staff.

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

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

10. STUDY ASSESSMENTS

10.1. Safety Assessments

10.1.1. Adverse Events

The collection of AEs is detailed in Section 11.2.

10.1.2. Vital Sign Measurement, Weight, and Height

Vital sign measurements (including blood pressure, heart rate, respiration, and oral temperature), height and ulnar length, and weight will be obtained at the time points specified in the Schedule of Events (Table 1).

During infusion of study drug, vital signs will be collected from the contralateral arm from which the blood samples are collected. Vital sign measurements will be monitored approximately CCI prior to infusion, and approximately CCI after the end of the infusion and then approximately every CCI thereafter up to CCI after the end of the infusion. In the absence of either a) IRRs (whether local or systemic) or b) other symptoms or signs of hypersensitivity associated with drug administration following CCI consecutive SRP-5051 administrations at the same dose level, collection of vital signs beyond CCI post-end of infusion is not required.

All measurements of vital signs will be performed after the patient has remained inactive for at least CCI. Pulse rate and respiratory rate are to be measured over CCI. For patients who are able to reach the supine position, blood pressure and pulse rate are to be measured after the patient has been supine for at least CCI. For patients who are unable to reach the supine position, blood pressure and pulse rate are to be measured with the patient in a consistent position throughout the study.

When vital sign measurements are scheduled at the same time as blood draws (CCI prior to the infusion), the blood draw will be obtained at the scheduled time point, and the vital signs will be measured prior to, but as close to, the scheduled blood draw as possible.

Temperature is to be recorded in degrees Celsius (°C) and weight is to be recorded in kilograms.

10.1.3. Physical Examination

Full physical examinations and limited physical examinations will be performed by the Investigator or qualified study staff at the applicable time points specified in the Schedule of Events (Table 1).

Full physical examinations will include examination of general appearance, head, ears, eyes, nose, throat, heart, chest (respiratory), abdomen (gastrointestinal), skin, lymph nodes, extremities, musculoskeletal, and neurological systems and will be performed CCI thereafter. Limited physical examinations will include cardiac, pulmonary, abdominal, and symptom-directed examination, and are to be performed CCI .

10.1.4. Clinical Laboratory Tests

The following routine clinical laboratory tests will be performed at the time points specified in the Schedule of Events (Table 1); refer to Section 10.1.4.1 below for instructions regarding unscheduled laboratory assessments. Clinical laboratory tests will be collected at the study site or at another convenient location, and will be analyzed centrally.

Routine clinical laboratory tests will be processed according to the Laboratory Manual provided for the study and will be analyzed by an accredited central laboratory selected by the Sponsor. Samples that are to be collected during dosing visits, as specified in the Schedule of Events (Table 1), will be collected prior to the study drug infusion, and may be obtained up to CCI prior to the infusion.

Chemistry: Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen, albumin, uric acid, total bilirubin, ALP, amylase, ALT, AST, GLDH, GGT, lactate dehydrogenase, C-reactive protein, and creatine kinase

Hematology: RBCs, total WBCs, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets

Coagulation screen: Prothrombin time, international normalized ratio, and activated partial thromboplastin time

QUA: pH, specific gravity, protein, glucose, ketones, cytology, and hemoglobin

Renal biomarkers: CCI albumin, UACR/UPCR

Other: eGFR, serum cystatin C, antiplatelet antibodies, serum complement, and CCI urine collection (including protein, albumin, and RBCs; at Baseline and again if required as per Section 9.3.2)

Refer to the Laboratory Manual for information on normal ranges.

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will determine whether abnormal assessment results are clinically significant or not clinically significant (as defined below in Section 10.1.5).

Serum cystatin C, QUA, and complement testing will be obtained every CCI. The first morning void will be used if possible. If serum cystatin C or QUA results are abnormal, unscheduled labs will be required and results reviewed prior to the next dose. Results must be reviewed and confirmed to meet the required thresholds prior to dosing at the subsequent visit, as described in Figure 3 and Section 9.3.2.

Additionally, on infusion visits, a local urine dipstick will be performed and results assessed prior to dosing. Unscheduled local QUA will be performed if urine dipstick results are abnormal as defined in Figure 2. Unscheduled central QUA, serum cystatin C, and CCI urine collection may be required if QUA results are abnormal, as defined in Figure 3 and Section 9.3.2.

10.1.4.1. Unscheduled Laboratory Assessments

Certain laboratory parameters may result in dosing delays, missed dose(s) (Section 9.2.2), or study drug discontinuation (Section 7.3). In the event of these abnormal laboratory results, additional safety laboratory assessment collections and monitoring are required.

Before study drug dosing may resume, these unscheduled laboratory assessments may require the patient to complete additional visits, or to have additional laboratory assessments collected at the patient's home or at another convenient location, for any or all of the following:

- Additional blood sample collection
- Additional spot urine sample collection
- CCI urine collection

10.1.5. Designation of Clinical Significance

A laboratory abnormality (Section 11.2.1) deemed clinically significant by the Investigator is to 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.

10.1.6. Electrocardiogram

A 12-lead ECG will be obtained in triplicate at the time points specified in the Schedule of Events (Table 1) and reviewed centrally. These ECGs will be performed at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling or study drug infusion). CCI

The Investigator will review the ECG results and determine if the findings are clinically significant.

10.1.7. Concomitant Medications, Procedures, and Therapies

Concomitant medications and procedures, changes in the dosage of concomitant medications, and concomitant therapies, including physiotherapeutic interventions, will be reviewed and recorded at each visit from the time the patient signs the informed consent form.

Refer to Section 9.5 for information about prohibited concomitant medications.

10.2. Pharmacokinetic Assessments

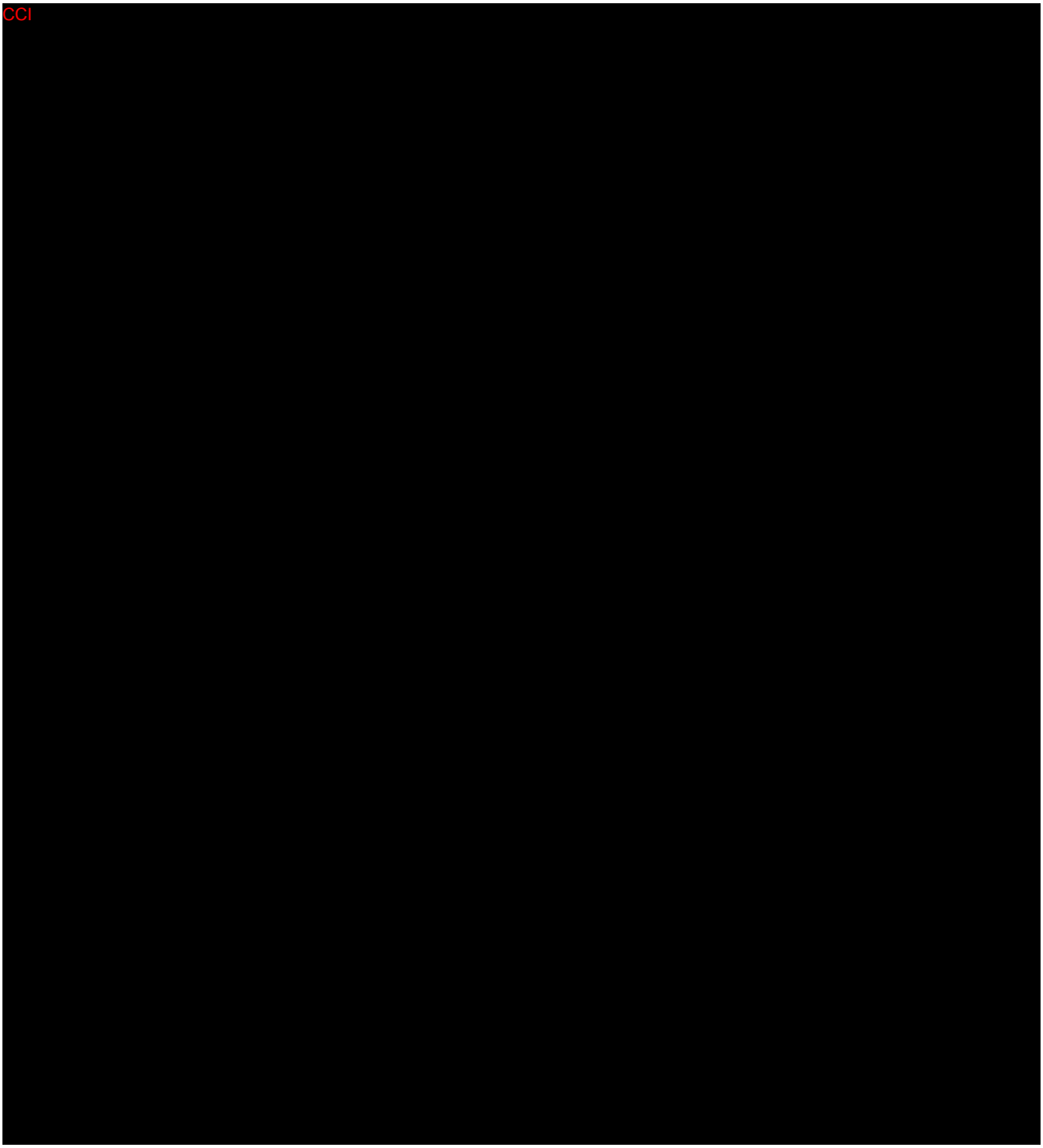
10.2.1. Blood Sample Collection

Plasma samples will be obtained at the time points specified in the Schedule of Events (Table 1), and are to be collected via peripheral venipuncture from the contralateral arm used for drug infusion. Plasma PK samples may not be collected from an IVAD.

Refer to the Laboratory Manual for additional details on handling and processing of plasma samples.

CCI

[redacted]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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 trial participant that does not necessarily have a causal relationship with the IP. An AE can, therefore, be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality that occurs during or after administration of an IP, whether or not considered related to the IP.

Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff
- The onset of new illness and the exacerbation of pre-existing medical conditions
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) deemed clinically significant (refer to Section 10.1.5 regarding designation of clinical significance)

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

11.1.2. Serious Adverse Event

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

- **Death**: The patient died as the result of the event.
- **Life-threatening event**: Any AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred (ie, does not include an AE that, had it occurred in a more severe form, might have caused death)
- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization.
    - Hospitalizations that are part of the study procedures are exempt unless the hospitalization is prolonged (based on the judgment of the Investigator) due to an event.
    - Pre-planned hospitalizations are not considered SAEs unless prolonged due to an AE.
- **Persistent or significant disability/incapacity**: An AE that results in persistent or significant disability or disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the study drug, or the partner of a patient exposed to the study drug.

- **Important medical event**: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

11.1.3. Adverse Events of Special Interest

The AESIs in this study are defined below in Sections 11.1.3.1 through 11.1.3.5, and are to be reported as instructed in Section 11.4.2.5. Refer to Section 9.2.2.1 for guidance on study drug dose interruption/delay in patients who meet certain laboratory criteria, and to Section 7.3 for the study stopping rules.

11.1.3.1. AESI Criteria for Liver Test Results

CCI [redacted]

11.1.3.2. AESI Criteria for Renal Test Results

CCI [redacted]

11.1.3.3. AESI Criteria for Hypersensitivity

CCI [redacted]

11.1.3.4. AESI Criteria for Platelet Count Results

CCI [redacted]

11.1.3.5. AESI Criteria for Rhabdomyolysis

CCI [redacted]

CCI [redacted]

11.1.4. Overdose

An overdose is defined as administration of a quantity of a medicinal product given (per administration or cumulatively) that is above the maximum recommended dose according to the authorized product information. Refer to Section 11.4.2.2 for specific guidance on overdose as it pertains to SRP-5051.

11.1.5. Medication Error

A medication error is any preventable incident that may cause or lead to inappropriate study drug use or patient harm while the study drug is in the control of the healthcare professional or, in certain cases, the patient. Such incidents may be due to healthcare professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, dispensing, nomenclature, compounding, distribution, administration, education, monitoring, and use.

11.1.6. Accidental/Occupational Exposure

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

11.2. Collection of Adverse Events

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by patient), 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 and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to Baseline or normal levels, the event has stabilized and there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died.

All AEs will be followed until the resolution of the AE, completion of the patient's study participation, or study termination, whichever occurs first. All SAEs will be followed until resolution or until the condition stabilizes or returns to Baseline status.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness recurs after resolution or worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF, as well as on the SAE Report Form's medical history section.

Patients who have received at least 1 dose of study drug and are withdrawn from treatment (Section 8.6) will be asked to complete an Early Termination visit (to complete the EOS assessments) approximately CCI [redacted] after their last dose of SRP-5051, or within CCI [redacted] of a withdrawal decision if early termination occurs after a missed dose. Any AEs are to be recorded through the EOS/Early Termination Visit.

For patients who are found to be ineligible for the study during the Screening 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 patient has completed participation in the study (Section 8.4), the Investigator or study staff becomes 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 10.1.5) by the Investigator is to be recorded as an AE. Whenever possible, the underlying medical diagnosis (eg, anemia) is to be recorded as the AE term. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result is to be obtained when clinically indicated.

11.2.2. Reporting Disease Progression

The event of disease progression 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 Investigational Product

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

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

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 is to assess the severity of all AEs using the **National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 5.0**.

Events **not listed in the CTCAE** are to 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 non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (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 sign-based abnormalities 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**.

11.3.5. Outcome of Adverse Events

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

11.3.6. Action Taken Regarding the Investigational Drug Product

The Investigator will provide information regarding the action taken with respect to the study drug in response to the AE. Categories for action taken regarding study drug will include "none", "drug interrupted", "drug withdrawn", and "not applicable".

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 SRP-5051 Investigator's Brochure.

11.4. Recording Adverse Events

All AEs from the time of providing signed informed consent/assent through the last follow-up visit will be recorded in each enrolled patient's eCRF. All SAEs will also be recorded on the SAE form and reported to the Sponsor within 24 hours of awareness. Other safety information, such as that pertaining to special situations (Section 11.4.2) and specified AESIs (Section 11.1.3), will also be recorded on the specified forms for reporting to the Sponsor within 24 hours of awareness.

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

Whenever possible, a diagnosis will be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. Several symptoms or laboratory results that are 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 is to be recorded as the AE.

Similarly, death is not an AE, but rather, the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then "death" must be reported as an AE.

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

Any SAE assessed as related to the study drug, occurring after the patient completes the study, should be recorded on an SAE 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

The Investigator must report all SAEs via email to PPD within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE, as per the information printed on the SAE form and in the SAE Completion guideline.

11.4.1.2. Suspected Unexpected Serious Adverse Reactions (SUSARs)

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 the requirements of the concerned competent authorities.

11.4.2. Reporting Special Situations

11.4.2.1. Pregnancy

Females have not been included in clinical trials of SRP-5051, and pregnant and/or lactating women have not been dosed with SRP-5051.

Patients in this study must follow the contraceptive requirements as outlined in Inclusion Criterion #3 (Section 8.2). If the female partner of a treated male patient becomes pregnant, the male patient must notify the Investigator within 24 hours of learning of the pregnancy. The Investigator must make every effort to ensure that the pregnant female is aware of the need to notify her healthcare provider regarding her male partner's participation in this clinical trial and his potential exposure to SRP-5051.

The study site staff must complete a pregnancy form and send to the Sponsor via email to PPD within 24 hours of learning of the pregnancy. The study site staff will make every effort to follow the pregnancy until the outcome is known.

11.4.2.2. Overdose

Currently, there is no basis for determining a clinically meaningful definition of overdose for SRP-5051. Therefore, as a preliminary criterion, an overdose is defined as administration of a dose CCI higher than the assigned dose per the protocol. For dose-calculation guidance, refer to the study-specific Pharmacy Manual.

An overdose is not an AE. An overdose must be reported even if it does not result in an AE. An overdose must be recorded on the appropriate form and sent to the Sponsor via email to PPD within 24 hours.

11.4.2.3. Medication Error

Any medication error is to be reported to the Sponsor on a specialized form sent via email to PPD within 24 hours of becoming aware, according to the process for reporting SAEs (Section 11.4.1).

11.4.2.4. Accidental/Occupational Exposure

Any accidental/occupational exposure (Section 11.1.6) is to be reported to the Sponsor on a specialized form sent via email to PPD 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 (Section 11.1.3) are to be reported on the appropriate form and sent to the Sponsor via email to PPD within 24 hours, according to the same guidance provided in Section 11.4.1 for reporting SAEs.

11.4.3. Miscellaneous

11.4.3.1. Unblinding Due to a Medical Emergency

Not applicable; this is an open-label study.

11.4.3.2. Responsibilities of the Investigator

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

- Monitoring and recording all AEs
- Determining the seriousness, severity, and relationship to IP, study procedure, and underlying disease for each AE
- Determining the onset and end date of each event
- Providing the initial report of all SAEs, special situations, and noted AESIs to the Sponsor 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

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

11.4.3.3. Responsibilities of the Sponsor

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

- Training of Investigator on AE/SAE 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

12. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

12.1. Recording of Data

Clinical data for this study will be captured in an electronic format. Electronic data capture will be provided by a contract research organization. The Investigator, or personnel delegated by the Investigator, will perform primary data collection/perform assessments based on the protocol design and capture in source documentation. Source documents are filed at the Investigator's site. All required study information must be recorded on the appropriate CRF screens/forms using the CRF Help Text. An eCRF must be completed for each patient that is enrolled. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The study monitor will conduct 100% source data verification to ensure maximum data integrity. All data must be carefully entered in a timely fashion to permit meaningful interpretation and study oversight.

12.2. Quality Assurance

The eCRFs will be reviewed at regular intervals by a clinical monitor from the Sponsor or a representative of the Sponsor per the agreed-upon 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, patient medical records, and other source documentation, IP dispensing records and IP storage area, study facilities, and any other source documentation.

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

12.3. Retention of Study Documents

At study completion, all eCRF data for an individual site will be copied onto a compact disc and provided to the Investigator for retention in the 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 patient 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.

13. STATISTICS

This section outlines the statistical analysis strategy and procedures for the study. Details of the statistical methods will be described in a separate technical document or in the Statistical Analysis Plan (SAP).

13.1. Analysis Endpoints

The study endpoints for evaluation are listed in Section 6.2.

13.2. Analysis Sets

The following analysis sets will be used for the primary and secondary endpoints in this study:

- **Safety Set**: The Safety Set is defined as all patients who enroll in the study and have started the study drug (SRP-5051) infusion. The dose group will be designated according to the actual dose received. This analysis set will be used for the safety analyses.
- **PK Set:** The PK Set is defined as all patients who enroll in the study, have started the study drug (SRP-5051) infusion, and have at least 1 PK concentration data collection. This analysis set will be used for the PK analyses.

The analysis sets be used for other endpoints and/or additional analyses will be defined in the SAP.

13.3. Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives of the study. CCI [redacted]

13.3.1. Safety Analyses

13.3.1.1. Adverse Events

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

All AEs will be classified as treatment-emergent AEs (TEAEs) or non-TEAEs. A TEAE is defined as an AE that emerges during treatment, having been absent pre-treatment, or worsens relative to the pre-treatment state. An AE that does not meet the TEAE definition will be classified as a non-TEAE.

Treatment-emergent AEs will be summarized using the number and percentage of patients reporting AEs, by MedDRA System Organ Class (SOC) and preferred term (PT), for each dose level and for the overall Safety Set. The ordering of AEs will be based on the AE rate in the overall Safety Set.

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

The following summary tables will be produced:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- SAEs
- AESIs
- AEs leading to study drug discontinuation
- AEs leading to death

The following listings will be produced:

- All TEAEs
- Non-TEAEs
- SAEs
- AESIs
- AEs leading to study drug discontinuation
- AEs leading to death

13.3.1.2. Other Safety Assessments

Clinical laboratory tests, vital signs, ECGs, weight and height, and any other procedures that are performed routinely as part of standard of care (eg, annual echocardiogram), as applicable, will be summarized descriptively. Additional details will be provided in the SAP.

13.3.1.3. Prior and Concomitant Medications

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

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

13.3.2. Pharmacokinetic Analyses

For all patients in the PK Set, plasma concentrations at predose, C_{max} (end of infusion), and approximately 4 to 6 hours postdose will summarized descriptively. Plasma concentration data may be evaluated and combined with clinical PK data from other clinical studies of SRP-5051.

CCI [redacted]

13.3.3. Summaries of Demographics, Baseline Characteristics, and Other Analyses

13.3.3.1. Patient Disposition, Demographics, and Baseline Characteristics

The number and percentage of patients completing or prematurely discontinuing from the study will be summarized. Reasons for premature discontinuation will also be summarized.

Demographic characteristics, including age (years), race, and ethnicity; Baseline characteristics, including height (cm), weight (kg), and body mass index (kg/m^2); CCI [redacted]

13.4. Interim Analysis

No formal interim analysis is planned.

13.5. Sample Size

The sample size for this LTE study will be determined by the number of patients who participate in other studies administering SRP-5051. Up to 60 patients are planned to enroll in this study upon completing a Phase 1 (ie, the completed Study 5051-101 [Section 5.4.1.1]) or Phase 2 (eg, the ongoing Study 5051-201 [Section 5.4.2.2]) study of SRP-5051 CCI [redacted]

14. ETHICS AND OTHER SPECIAL REQUIREMENTS

14.1. Compliance with Ethical and Regulatory Guidelines

This study will comply with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, ICH E6 (R2) GCP Guideline, and applicable national regulations such as the European Clinical Trial Directive 2001/20/EC, European Union Clinical Practice Directive 2005/28/EC, and principles of GCP described in 21 Code of Federal Regulations parts 50, 54, 56, and 312.

14.2. Institutional and Ethics Review

Before enrollment of patients into the study, the protocol and informed consent (for study participants or parents/legal guardians, if applicable) and informed assent (for patients, if applicable) documents will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol and all substantial changes to the trial documentation will be subjected to the same IRB/IEC and regulatory authority review requirements as the original study protocol.

The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the IP during the study. Institutional Review Board approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted.

All correspondence with the IRB/IEC and the regulatory authority must be retained in the study regulatory files.

14.3. Informed Consent

Informed consent from each patient's parent(s) or legal guardian(s) and informed assent from each patient, if applicable, must be obtained before any study-specific Screening or Baseline Period evaluations are performed. One copy of the signed informed consent/assent documents will be given to the patient; 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.

14.4. 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 patient, and are deemed by the Investigator as crucial for the safety and well-being of that patient, may be instituted for that patient only and documented as deviations. The Investigator will contact the Medical Monitor as soon as possible regarding such a deviation. These departures do not require 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.

14.5. 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 patient's parent(s) or legal guardian(s), or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current global data protection standards (eg, Health Insurance Portability and Accountability Act, General Data Protection Regulation).

Patients will be referenced by an assigned patient identification number on the eCRFs and other data collected by the Sponsor. The Investigator must maintain all documents related to the study that identify the patient (eg, the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB/IEC, the study monitor, or the Sponsor or its representatives.

15. STUDY DOCUMENTATION AND GENERAL INFORMATION

15.1. Essential Study Documents

Essential study documents are among the critical documents required before study enrollment is to occur. Essential documents, 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: patient 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 (IND) safety reports/ Safety Alert Letters/SUSARs.

15.2. General Information

The Investigator should be familiar with and refer, as needed, to the current SRP-5051 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.

15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by the Sponsor. At the conclusion of this clinical study, a clinical study report will be prepared. In addition, a manuscript may be prepared for publication in a reputable scientific journal under the direction of the Sponsor. The Sponsor will publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by the Sponsor, as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov 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 shall not be published or disclosed to a third party without the prior written consent of the Sponsor. The primary publication from this study will report the results of the study in accordance with the current "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations.

The publications committee established by the Sponsor will oversee this process. Additional publications may follow. 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 course of the study related to the quality of the IP, the Investigator, clinical site pharmacist, or pharmacy designee should contact the Sponsor or designated contract research organization.

16. LIST OF REFERENCES

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