CLINICAL STUDY PROTOCOL

DRUG:	SRP-4045 Injection and SRP-4053 Injection
STUDY NUMBER:	4045-301
STUDY TITLE:	A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy
IND NUMBER:	118,086 (SRP-4045) 119,982 (SRP-4053)
EUDRACT NUMBER:	2015-002069-52
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	Version 6 (Amendment 5), 03 April 2017
REPLACES VERSION DATE:	[redacted]

CONFIDENTIALITY STATEMENT

those individuals to whom the drug may be administered. These restrictions will continue to apply after the study has closed.

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy
Study No:	4045-301
Current Version Date:	Version 6, 03 April 2017

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 products (IPs).
- The ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312 and the European Clinical Trial Directive 2001/20/EC.

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

Edward M. Kaye, MD
President & Chief Executive Officer,
Chief Medical Officer
Sarepta Therapeutics Inc.
215 First Street
Cambridge, MA 02142 USA

Date

INVESTIGATOR'S AGREEMENT

I have read Study No. 4045-301 (Version 6) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Responsible Physician	[redacted]	[redacted]

1. SYNOPSIS

NAME OF COMPANY Sarepta Therapeutics Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCTS:** SRP-4045 Injection and SRP-4053 Injection **NAME OF ACTIVE INGREDIENTS:** SRP-4045 and SRP-4053
TITLE: A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy	
Study Number: 4045-301	
Phase of Study: PHASE 3	
INVESTIGATOR STUDY SITES: This is a multinational clinical trial to be conducted at approximately 40 study sites.	

OBJECTIVES:

Double-Blind Treatment Period

Primary Objective:

The primary objective of this study is to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) compared to placebo on ambulation, endurance, and muscle function as measured by the 6-minute walk test (6MWT).

Secondary Objectives:

The secondary objectives are to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on:

- Dystrophin protein expression in biopsied muscle tissue as measured by:
  - Western blot (quantification)
  - Immunohistochemistry (IHC) fiber intensity
- Functional status as measured by:
  - Ability to rise independently from the floor (without external support)
  - Loss of ambulation (LOA)
  - North Star Ambulatory Assessment (NSAA)
  - Respiratory muscle function, as measured by forced vital capacity (FVC) % predicted
  - Frequency of falls
  - Cardiac function, as measured by left ventricular ejection fraction (LVEF)
- Safety and tolerability of SRP-4045 and SRP-4053

[redacted]

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[redacted]

Open- abel Treatment Period

Objectives of the open-label (OL) study period:

- Evaluate the long-term effects of SRP-4045 and SRP-4053 treatment on functional status up to 192 weeks. Evaluate the long-term safety and tolerability of SRP-4045 and SRP-4053.
- [redacted]

Pharmacokinetic Objective

The pharmacokinetic (PK) objective is to evaluate the PK properties of SRP-4045 and SRP-4053 using a population PK model.

METHODOLOGY:

This is a double-blind, placebo-controlled, multicenter study with an OL extension to evaluate the efficacy and safety of 2 phosphorodiamidate morpholino oligomers (PMOs), SRP-4045 and SRP-4053, in approximately 99 patients with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 and 53, respectively. A placebo group will be employed, and patients will be randomized in a double-blind fashion in a 2:1 ratio, combined active (SRP-4045 or SRP-4053) to placebo. [redacted]

Double-Blind Treatment Period

Patients will be evaluated for inclusion during a Screening period [redacted]. Eligible patients who have out-of-frame deletions amenable to exon 45 or 53 skipping will be randomized in a 2:1 ratio between the active group and the placebo group to receive once weekly intravenous (IV) infusions of study treatment for up to 96 weeks. DMD patients amenable to exon 45 skipping will be randomized in a 2:1 ratio to receive either SRP-4045 or matching placebo, and DMD patients amenable to exon 53 skipping will be randomized in a 2:1 ratio to receive either SRP-4053 or matching placebo. Thus, SRP-4045 and SRP-4053 will each be administered as monotherapy only, and not co-administered. [redacted]

Efficacy, including the 6MWT, NSAA, and pulmonary function tests (PFTs), will be assessed at regularly scheduled study visits and safety will be monitored on an ongoing basis for all patients. Upon qualification for the study based on Screening and Baseline assessments and after eligibility is confirmed by both the [redacted] Site and the Sponsor, all patients will undergo a muscle biopsy at Baseline. A second biopsy will be performed at Week 48. [redacted]

Data Monitoring Committee and Interim Analyses

An independent Data Monitoring Committee (DMC) will be formed to assist in the periodic monitoring of safety, data quality, and integrity of study conduct, as well as to evaluate an interim analysis of efficacy. This interim analysis is intended to minimize the duration of placebo exposure if adequate evidence of efficacy is established at the interim analysis. The first DMC meeting is planned to be held 6 months after treatment initiation for the first patient in the study and approximately every 6 months thereafter throughout the study. At each DMC meeting, the DMC will review cumulative safety data and make one of the following recommendations: study may proceed as

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planned, resume study with major/minor modifications (to be specified), temporarily suspend enrollment and/or dosing pending further DMC evaluation, or permanently discontinue the study.

The interim analysis of efficacy will be performed when Week 48 6MWT data are available for 75% of patients [redacted] If efficacy is clearly demonstrated on 6MWT and safety results are acceptable, the DMC will recommend stopping the double-blind placebo-controlled period early and start OL treatment for all patients. If the interim analysis does not meet the required criteria, the DMC will recommend continuing the double-blind placebo-controlled study period to Week 96.

Pharmacokinetic Assessments

[redacted] blood samples for assessing plasma drug concentrations will be obtained [redacted].

Safety Assessments

Safety will be assessed through the collection of adverse events (AEs), laboratory tests, immunogenicity, electrocardiograms (ECGs), vital signs, and physical examinations throughout the study as described in the Schedule of Events.

Open-Label Treatment Period

Upon completion of the double-blind portion of this study, patients may participate in an OL treatment extension period of up to 96 weeks in which they will receive weekly treatment with 30 mg/kg SRP-4045 or SRP-4053, according to genotype.

Functional assessments, including the 6MWT, will be assessed at regularly scheduled study visits and safety will be monitored on an ongoing basis for all patients up to Week OL96. Safety will be assessed in the same manner as during the Double-Blind Treatment Period, as described in the Schedule of Events.

[redacted] blood samples for assessing plasma drug concentrations will be obtained [redacted]

All participating patients will be assessed for safety at an End of Study visit [redacted].

Duration of Study:

Screening/Baseline Period: [redacted]

Double-Blind Placebo-Controlled Treatment Period: Up to 96 weeks, or less (depending on the outcome of an interim analysis at Week 48).

Open-Label Treatment Period: Up to an additional 96 weeks. Safety Follow-up Period: Approximately 4 weeks (28 days) following last infusion.

Total patient participation: Up to 204 weeks

NUMBER OF PATIENTS: Approximately 99 eligible patients will be included in this study in a first-come, first-to-be-enrolled fashion. Randomization will be carried out separately in each of the 2 genotypes (SRP-4045 or SRP-4053) using a 2:1 ratio between the active group (to receive SRP-4045 or SRP-4053, according to the patient's pre-existing genotype report; approximately 66 patients) and the placebo group (approximately 33 patients). [redacted]

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INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

A patient must meet all of the following criteria to be eligible for this study.

1. Is a male with an established clinical diagnosis of DMD and an out-of-frame deletion amenable to:
   - Exon 45 skipping [redacted] OR
   - Exon 53 skipping [redacted]

   [redacted] he patient's amenability to exon 45 or 53 skipping must be confirmed prior to first dose using the genotyping results obtained during Screening.
2. Is between 7 and 13 years of age, inclusive, at randomization.
3. Has stable pulmonary function (FVC % of predicted ≥50% and no requirement for nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Has intact right and left biceps brachii muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Has been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks [redacted]
6. [redacted]
7. Achieved a mean 6MWT distance of ≥300 to ≤450 meters [redacted]
8. 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 (eg, male condom or female oral contraceptives) during this time frame.
9. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.
10. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the patient to participate in the study.

Exclusion Criteria

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

1. Treatment with any of the following investigational therapies according to the time frames specified:
   [redacted]
   - Utrophin upregulating agents (eg, ezutromid [SMT C1100] or other)

     [redacted]

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[redacted]

- PRO045 (BMN 045)
- PRO053 (BMN 053)

[redacted]

2. Treatment with any of the following non-investigational therapies according to the time frames specified:
   - Within 12 weeks prior to Week 1:
     - [redacted]
3. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable.
4. Presence of any other significant genetic disease other than DMD (eg, dwarfism).
5. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
6. LVEF <50% on the Screening echocardiogram (ECHO) [redacted]
7. [redacted]
8. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, patients who seem unable / unwilling to comply with the study procedures, in the Investigator's opinion, are to be excluded.

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DOSE/ROUTE/REGIMEN (TEST ARTICLE):

SRP-4045 or SRP-4053 (each at 30 mg/kg) will be administered according to genotype as an IV infusion over approximately 35-60 minutes once a week for up to 96 weeks, followed by up to 96 weeks of OL treatment with SRP-4045 or SRP-4053 according to genotype at 30 mg/kg/week.

In the event it becomes necessary, venous access methods such as midline catheter, central line, or portacath may be used at the Investigator's discretion, contingent upon approval by local and/or country-specific regulatory body(ies).

REFERENCE TREATMENT:

Matching placebo (phosphate buffered saline) will be administered as an IV infusion over 35-60 minutes once a week for up to 96 weeks. Dosing calculations will be based on a dose of 30 mg/kg.

CRITERIA FOR EVALUATION:

Efficacy:

Primary Endpoints:

- [redacted]
- Change from Baseline at Week 96 in 6MWT.

Secondary Endpoints:

- Change from Baseline at Week 48 in the quantity of dystrophin protein expression as measured by Western blot of biopsied muscle tissue.
- Change from Baseline at Week 48 in the intensity of dystrophin expression in biopsied muscle tissue, as measured by IHC.
- Ability to rise independently from the floor (without external support) at Week 96 [redacted]
- Time to LOA from randomization through Week 96.
- Change from Baseline at Week 96 in:
  - NSAA total score
  - forced vital capacity percent predicted (FVC%) predicted
  - Frequency of falls
  - LVEF

[redacted]

Safety:

The safety and tolerability of SRP-4045 and SRP-4053 will be assessed through a review and evaluation of: AEs, serious adverse events (SAEs), deaths and discontinuations due to AEs; laboratory testing including hematology,

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coagulation, chemistry [redacted] and urinalysis [redacted]; immunogenicity assessments; ECG; vital signs; and physical examination findings.

Pharmacokinetics:

Pharmacokinetic parameters will be estimated by population PK analysis. [redacted]

STATISTICAL METHODS

Sample Size:

[redacted]

Efficacy Analyses:

The primary analyses of the efficacy endpoints will be performed on the Intent-to-Treat (ITT) analysis set, which consists of all randomized patients, with treatment group designated according to randomization treatment assignment. All efficacy endpoints will be summarized descriptively by visit, if appropriate.

Analyses of the Primary Efficacy Endpoints

At the interim analysis, the primary efficacy endpoint will be the change from Baseline at Week 48 in 6MWT. At the final analysis, the primary efficacy endpoint will be the change from Baseline at Week 96 in 6MWT.

[redacted]

Analyses of the Secondary Efficacy Endpoints

[redacted]

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[redacted]

Interim efficacy analysis

An interim efficacy analysis will be performed when Week 48 6MWT data are available for 75% of the patients [redacted]

Safety Analyses:

Treatment-emergent adverse events (TEAEs) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group. Non-treatment-emergent events will be recorded in the data listings. For all AE tables, the number and percentage of patients reporting AEs will be grouped by SOC and PT. Multiple occurrences of the same AE at the PT (or SOC) level in the same patient will be counted only once in the calculation of the number and percent of patients reporting AEs for each PT (or SOC). If a patient experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship to study treatment or maximum severity will be used to summarize AEs by relationship and severity.

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

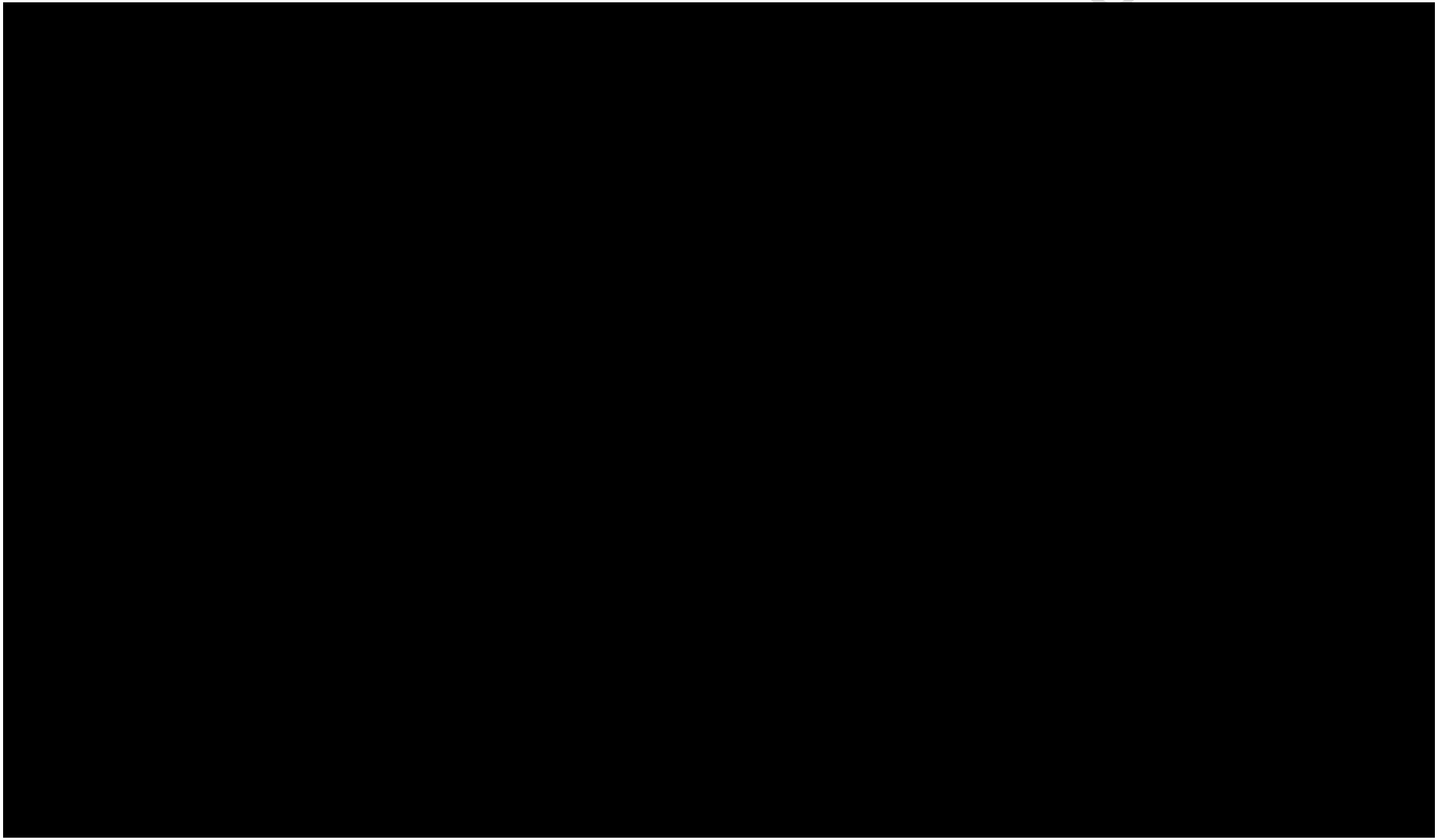
Pharmacokinetic Analyses:

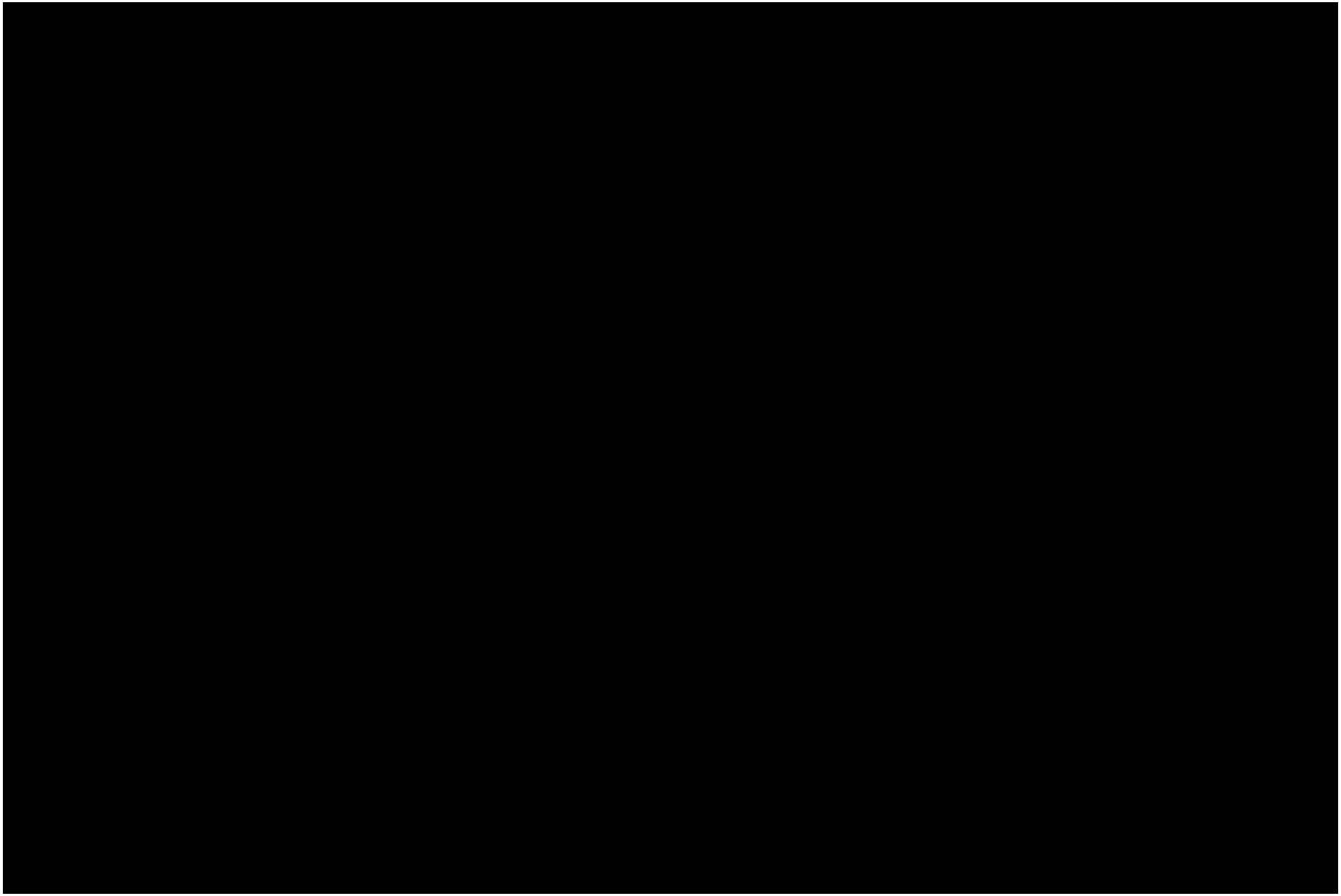
Individual plasma levels of SRP-4045 and SRP-4053 will be listed with the corresponding time related to study treatment administration, and summary statistics will be generated by per-protocol time of collection.

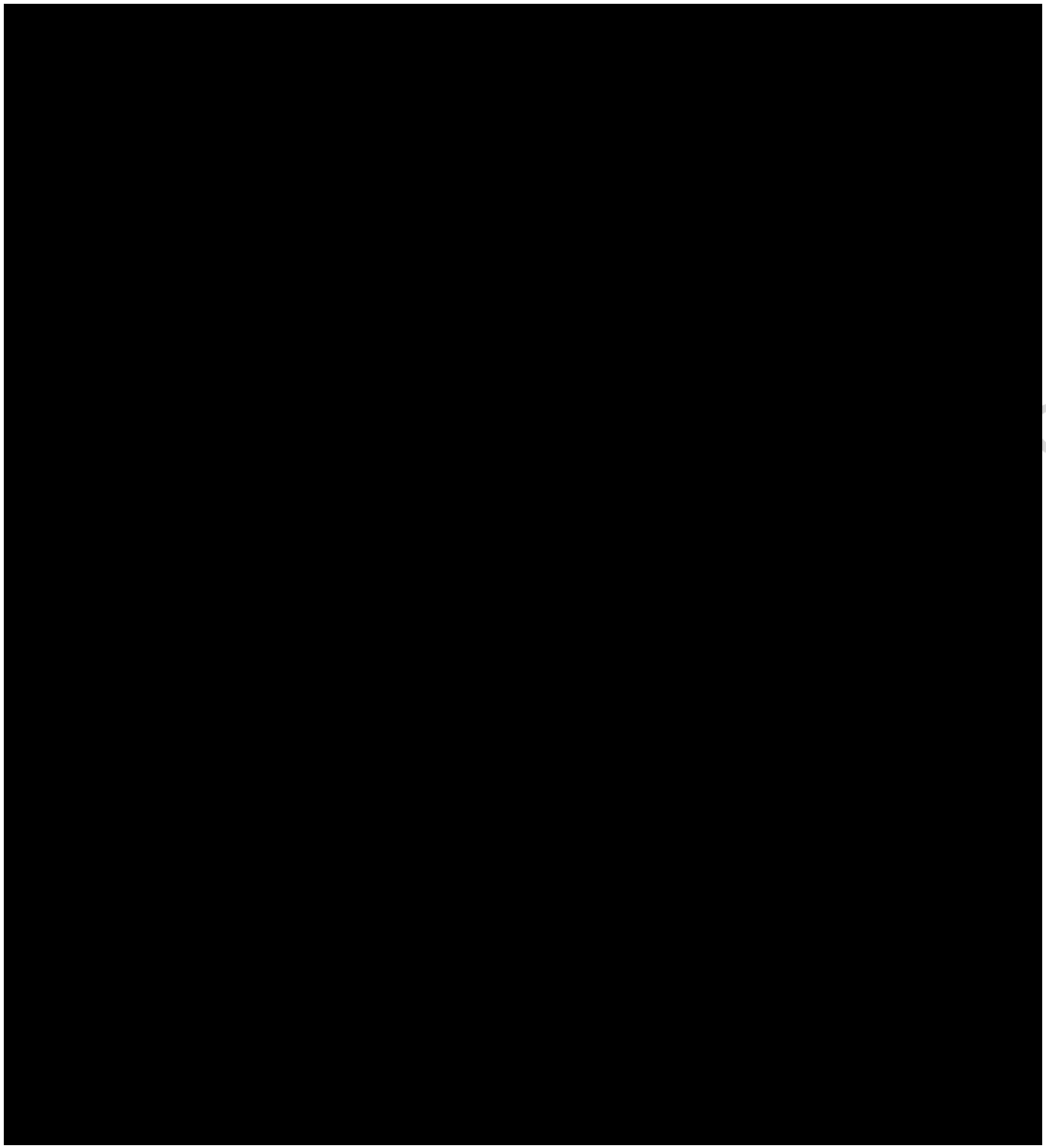
Population PK analysis of plasma concentration-time data of SRP-4045 and SRP-4053 will be performed [redacted] The population PK analysis will be presented in a separate technical document.

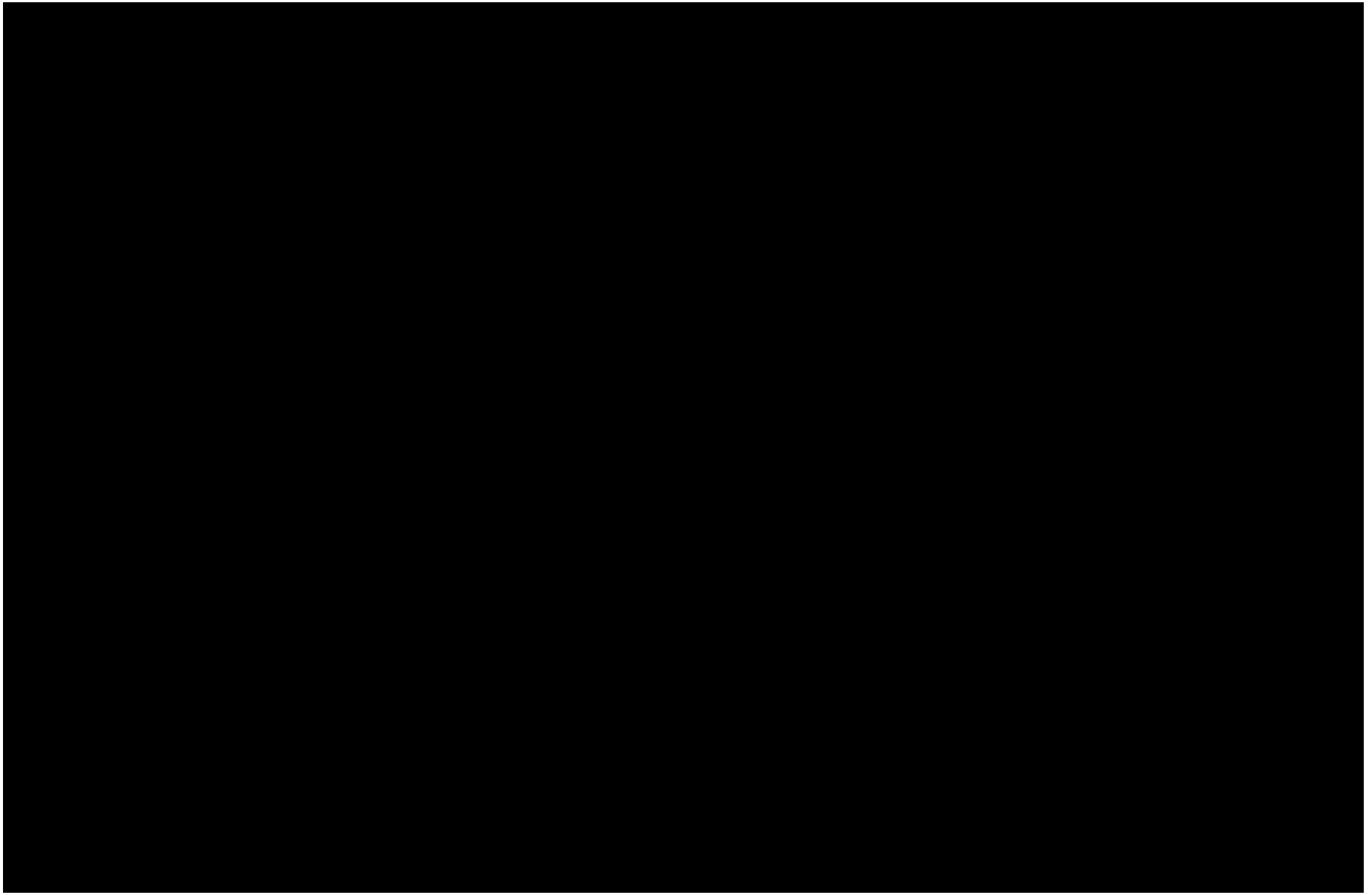
2. SCHEDULE OF EVENTS

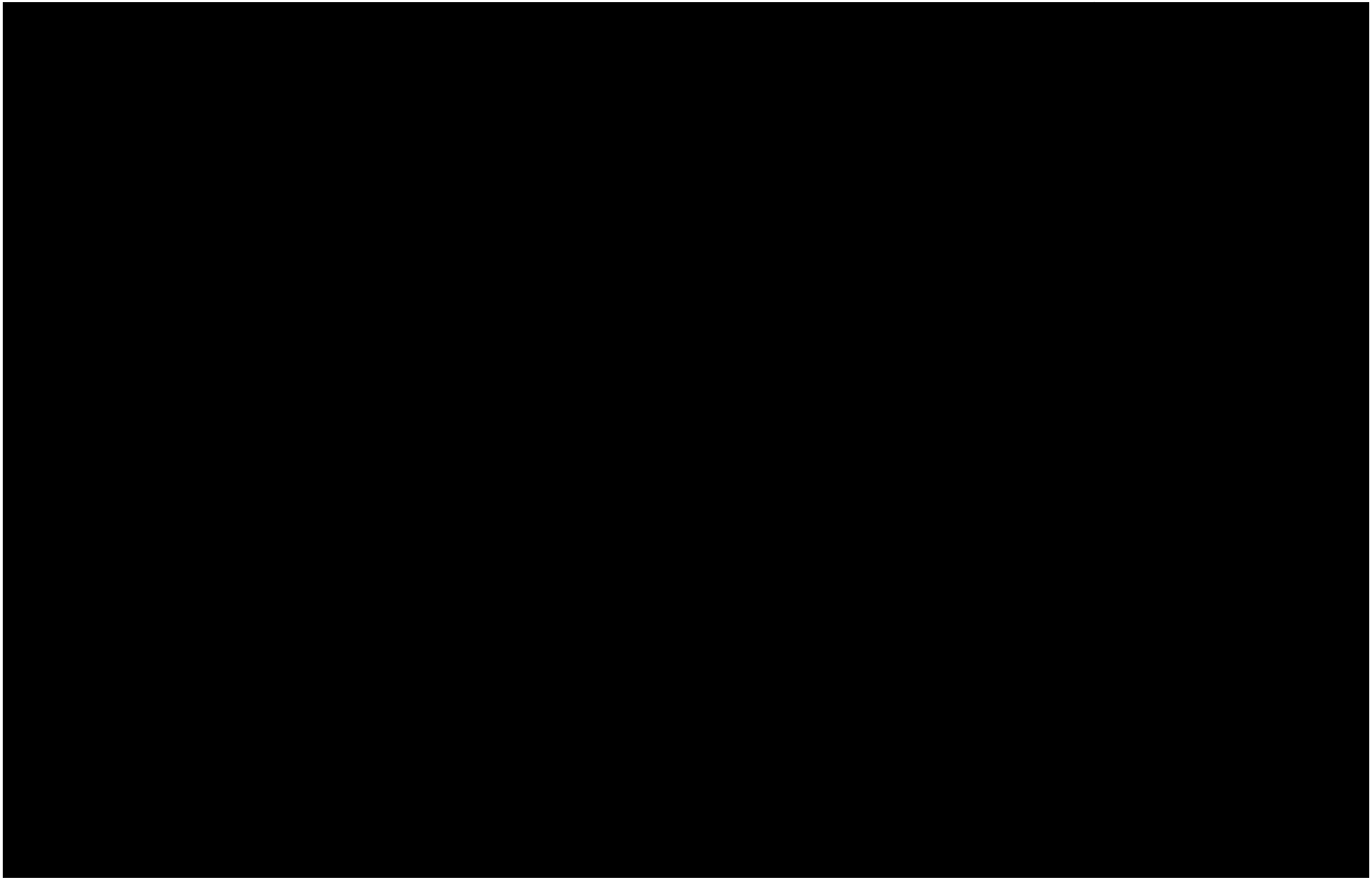
Table 2: Double-Blind Placebo-Controlled Treatment Period

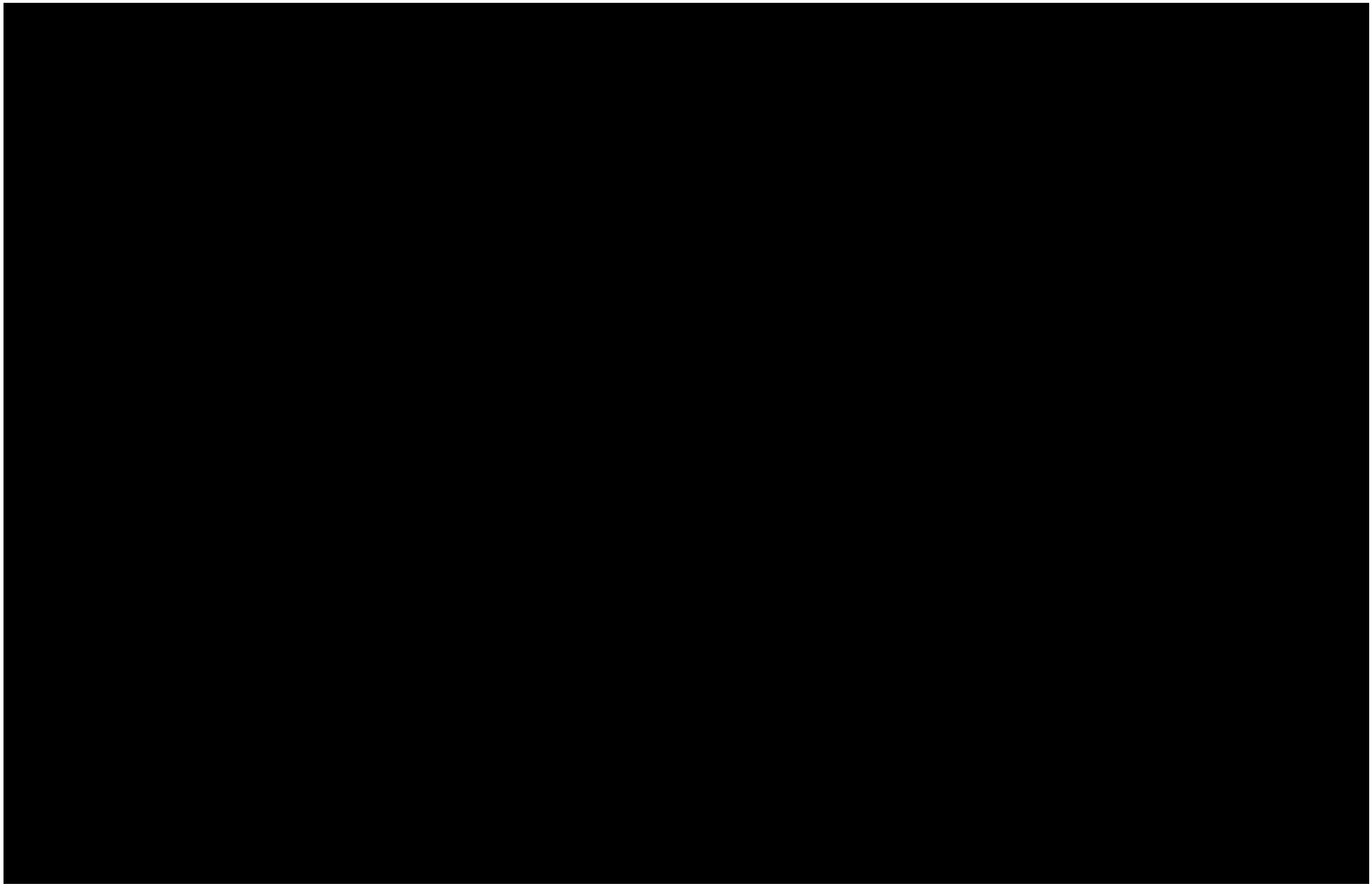












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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2D	2-dimensional
6MWT	6-minute walk test
AAOS	American Academy of Orthopaedic Surgeons
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocking agent
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BUN	blood urea nitrogen
CD	compact disc
CFR	Code of Federal Regulations
[redacted]	[redacted]
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
DMC	Data Monitoring Committee
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
ECG(s)	electrocardiogram(s)
ECHO(s)	echocardiogram(s)
EDC	electronic data capture
FDA	Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HEENT	head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Definition
IHC	immunohistochemistry
IND	Investigational New Drug
Injection	US nomenclature equivalent to Concentrate for Solution for Infusion
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous, intravenously
IVR	interactive voice response
[redacted]	[redacted]
LDH	lactate dehydrogenase
LOA	loss of ambulation
[redacted]	[redacted]
LVEF	left ventricular ejection fraction
[redacted]	[redacted]
MedDRA®	Medical Dictionary for Regulatory Activities®
MEP	maximum expiratory pressure
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
NCS	not clinically significant
NHP	Nonhuman primates
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
NSAA	North Star Ambulatory Assessment
OL	open-label
PBS	phosphate-buffered saline
PDPF	percent dystrophin-positive fibers
PFT(s)	pulmonary function test(s)
PK	pharmacokinetics
PMO	phosphorodiamidate morpholino oligomer
[redacted]	[redacted]
PT	preferred term
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cell

5. INTRODUCTION

5.1. Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked degenerative neuromuscular disease caused by mutations in the dystrophin gene. DMD occurs in approximately 1 in 3500-5000 males worldwide (CDC 2009; Sarepta Therapeutics Inc., Data on File). 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 the protein complex that connects the cytoskeleton of a muscle fiber to the cell membrane and extracellular matrix and acts to prevent muscle membrane damage during eccentric contraction. In the absence of dystrophin, the stress of muscle eccentric contraction causes widespread, chronic and progressive muscle damage and ultimately replacement by fat and fibrotic tissue. The clinical effect of this disrupted dystrophin reading frame is thus ultimately fatal.

Duchenne muscular dystrophy is usually first diagnosed between the ages of 3 to 5 years (Ciafaloni 2009), when toddlers develop a waddling gait, lordosis, toe walking, calf hypertrophy, and difficulty climbing stairs. Over time, ambulation becomes increasingly abnormal. By 8 years of age, most patients lose the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking, leading to the increased use of mobility devices such as strollers and scooters. Patients with DMD spend less time walking than healthy boys and walk more slowly than healthy boys (McDonald 2005), and are significantly less active than healthy boys of similar age (McDonald 2002, McDonald 2005). By 10 to 14 years of age, most boys lose ambulation and are wheelchair bound. Current treatments for DMD have a modest impact on disease outcomes. These include corticosteroids, which can prolong ambulation and reduce the incidence of severe scoliosis; however, they are often associated with serious side effects (Biggar 2006; Manzur 2004) and are not always employed.

In addition to progressive muscle weakness and wasting, manifestations of DMD typically include cardiac and pulmonary symptoms in addition to several well-understood laboratory abnormalities. While pulmonary and cardiac functions are generally normal during early childhood, they progressively worsen over time, and patients typically die from cardiac or respiratory failure in their 20s (Brooke 1989, Eagle 2002).

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

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

In addition to the clinical manifestations, patients with DMD have grossly elevated 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 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 (LDH) levels, originating from degenerating muscle, are also generally observed in these patients (McMillan 2011). Creatinine levels tend to be low or low normal due to decreased muscle mass (Viollet 2009), thus serum cystatin C may provide a better measure of renal function than does creatinine.

5.2. Phosphorodiamidate Morpholino Oligomers (PMOs) for the Treatment of Duchenne Muscular Dystrophy

Ribonucleic acid (RNA) therapeutics are compounds composed of heterocyclic nucleobases (adenine, cytosine, guanine, and thymine, or analogues) linked together on an oligomer backbone that supports hybridization via Watson-Crick base pairing with specific complementary RNA targets. RNA therapeutics can be synthesized to bind targeted RNA sequences in a pathogen or pathogenic process to treat a wide range of diseases through positively or negatively modulating gene expression. A relatively new use of RNA therapeutics is to target a pre-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. 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 (DNA). Moreover, the morpholine rings are linked through neutrally charged phosphorodiamidate moieties as opposed to negatively charged phosphodiester linkages in RNA and DNA. These differences were designed to increase stability and address safety issues seen with some earlier oligonucleotide backbone chemistries.

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

The investigational drug products, SRP-4045 and SRP-4053, are PMOs that selectively bind to a regulatory site governing splicing of exon 45 or exon 53, respectively, in dystrophin pre-mRNA and cause the exon to be skipped during processing. These investigational products (IPs) were designed for use in patients with mutations amenable to skipping exon 45 or exon 53 each of which represent approximately 8% of all DMD patients (Aartsma-Rus 2009).

5.3. Nonclinical Studies with SRP-4045 and SRP-4053

A series of nonclinical studies were performed with SRP-4045 and SRP-4053, which evaluated their in vitro pharmacokinetic (PK) and metabolism properties, safety pharmacology, toxicity/toxicokinetics, and genotoxicity. All safety pharmacology and toxicity studies considered necessary for human safety assessment were conducted in compliance with Good Laboratory Practice regulations. In addition, nonclinical safety studies have been performed with AVI-4225, which is another exon-skipping PMO for restoration of dystrophin production with the same mechanism of action and similar physicochemical properties. The differences between this PMO, SRP-4045, and SRP-4053 are the specific nucleobase sequence and the number and proportion of specific nucleobases in each oligomer.

SRP-4045 and SRP-4053 have demonstrated low protein binding and low potential for drug-drug interactions because they are not metabolized and do not interact with cytochrome P450 isoenzymes at biologically relevant concentrations. In nonclinical safety studies of SRP-4053 and SRP-4045, no cardiovascular or central nervous system effects, genotoxicity, male reproductive toxicity, or evidence of immunotoxicity were detected. The kidney was the main target organ after once-weekly intravenous (IV) injections in repeat-dose toxicity studies; this finding is consistent with renal excretion being the major elimination pathway. [redacted] No renal or bladder findings were observed in the 12-week study of SRP-4053 in cynomolgus monkeys and the NOAEL was the highest dose tested (320 mg/kg). [redacted] Plasma exposure (maximum observed plasma concentration, area under the concentration-time curve) of SRP-4053 and SRP-4045 was high, increased with increasing dose in all species tested ([redacted] monkeys), and there was no evidence for significant plasma accumulation after repeated dosing in animals. No adverse renal findings have been observed at the highest dose levels tested for SRP-4045 in [redacted] monkeys (320 mg/kg, which was the NOAEL) after 12 weeks of once-weekly IV injections, [redacted]

Further details of the nonclinical studies for SRP-4045 and SRP-4053 are described in the respective Investigator's Brochures.

5.4. Clinical Experience with SRP-4045 and SRP-4053

SRP-4045

To date, one clinical study (Study 4045-101) has been initiated to evaluate SRP-4045 in humans. This is a randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and

PK study, followed by an open-label (OL) safety and efficacy evaluation of SRP-4045 in patients with advanced-stage DMD amenable to exon 45 skipping. This study is being conducted in the United States (US).

As of 03 October 2016, 12 patients had received 1 or more doses of SRP-4045 or placebo; patients had received doses up to 30 mg/kg of SRP-4045 in this study. No deaths, overdoses, or discontinuations from the study due to an adverse event (AE) had been reported. There had been no treatment-related serious adverse events (SAEs) and no serious infusion-related reactions or hypersensitivity events. The profile of treatment-emergent adverse events (TEAEs) had been consistent with the use of a medical device (ie, central venous access port) and for a patient population with advanced stage DMD.

Refer to the Investigator's Brochure for additional clinical data for SRP-4045.

SRP-4053

To date, one clinical study (Study 4053-101) has been initiated to evaluate SRP-4053 in humans. This study is a 2-part, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and PK study (Part 1) followed by an OL safety and efficacy evaluation (Part 2) in patients with DMD amenable to exon 53 skipping. The study is being conducted in the European Union. Part 1 of the study has been completed (12 patients), and the Data Monitoring Committee (DMC) recommended proceeding to Part 2, in which patients are receiving doses of 30 mg/kg SRP-4053 administered once-weekly via IV infusion. Part 2 is currently ongoing.

As of 03 October 2016, 25 patients had received treatment with SRP-4053 and had preliminary safety data. No deaths, overdoses, or discontinuations from the study due to an AE had been reported. There had been no treatment-related SAEs and no serious infusion-related reactions or hypersensitivity events. No patterns or trends had been identified for TEAEs, and the profile of TEAEs was consistent with a patient population with DMD.

Refer to the Investigator's Brochure for additional clinical data for SRP-4053.

5.5. Rationale for the Current Study

The purpose of this study is to evaluate the efficacy and safety of SRP-4045 and SRP-4053 administration in DMD patients with deletion mutations amenable to treatment by exon 45 or exon 53 skipping, respectively.

DMD is a progressive disease that leads to relentless deterioration of muscle function and is ultimately fatal. As there is no approved therapy for DMD patients with mutations amenable to exon 45 or exon 53 skipping, there is a high unmet medical need for effective treatments. SRP-4045 and SRP-4053 have the potential to be disease-modifying treatments for boys with DMD mutations amenable to exon 45 and exon 53 skipping, respectively.

As summarized in Section 5.2 and Section 5.4 and in the SRP-4045 and SRP-4053 Investigator's Brochures, the totality of the nonclinical data with these PMOs as well as AVI-4225 suggests that the most likely target organ for toxicity is the kidney, which can be clinically monitored. The safety margins are acceptable for once-weekly IV administration at the proposed 30 mg/kg dose. These data warrant the clinical development of SRP-4045 and SRP-4053 for DMD patients amenable to skipping exons 45 and 53, respectively.

5.6. Benefit and Risk Summary

Study 4045-301 (ESSENCE) is designed to investigate the efficacy and safety of SRP-4045 and SRP-4053 in DMD patients with out-of-frame deletion mutations amenable to exon 45 and exon 53 skipping, respectively. No therapies are currently available for these genetic subgroups, which each comprise approximately 8% of all DMD patients. SRP-4045 and SRP-4053 are PMOs designed to promote alternative splicing of the dystrophin transcript to restore the reading frame, permitting production of an internally truncated form of dystrophin protein.

In nonclinical studies of SRP-4045 and SRP-4053, the kidney was the primary route of clearance and the kidney was identified as the main target organ for toxicity in rodents and nonhuman primates (NHPs). Renal findings with SRP-4045 were all non-adverse at the highest dose levels tested in [redacted] NHPs (320 mg/kg) which resulted in plasma exposures based on area under the curve (AUC) that were [redacted]old greater than human plasma exposure at the 30-mg/kg dose. For SRP-4053, [redacted] plasma exposures at the NOAEL in NHPs (320 mg/kg) were 27-fold greater than human plasma exposure at the 30-mg/kg dose.

Given that the kidney was identified in nonclinical studies as a potential target organ for human toxicity, the Sponsor has determined renal toxicity to be a safety topic of special interest, and Study 4045-301 will monitor renal function closely via serum and urinary biomarkers.

Both SRP-4045 and SRP-4053 have been studied in DMD patients at weekly doses of 30 mg/kg IV, the same dose to be used in the present study. As of 03 October 2016, 25 patients had received 30 mg/kg SRP-4053 for at least 24 weeks in the Phase 1/2 Study 4053-101 and 12 patients in the Phase 1 Study 4045-101 had received SRP-4045 for at least 24 weeks. The 12 patients in Study 4045-101 had been randomized and treated with once-weekly IV infusions of placebo (n = 4) or SRP-4045 (n = 8) in escalating doses (4 mg/kg for 2 weeks, 10 mg/kg for 2 weeks, 20 mg/kg for 2 weeks, and 30 mg/kg for at least 6 weeks and until rollover was allowed into the OL extension period). To date, there have been no signals of renal toxicity or any other end-organ toxicity for SRP-4053 or SRP 4045. In addition, no deaths, overdoses, or discontinuations from the studies due to an AE have been reported. There have been no treatment-related SAEs and no serious infusion-related reactions or hypersensitivity events. A data safety monitoring board has performed 2 reviews of safety data during each clinical trial and has identified no safety signal that would indicate that patients should not continue to be dosed at 30 mg/kg/week.

In Study 4045-301 (ESSENCE), patients will undergo 2 muscle biopsies, one at baseline and one at Week 48 of the double-blind, placebo-controlled treatment period. Because of the intended mechanism of action of SRP-4053 and SRP-4045, dystrophin production in muscle is a key efficacy endpoint and requires sampling of muscle tissue. While muscle biopsy procedures entail potential risk, the Sponsor has taken careful measures to mitigate such risks in study patients. Biopsies will be performed only at top-tier medical institutions by surgeons and anesthesiologists with expertise in the specialized surgical management required by DMD patients and who have received study-specific training by the Sponsor.

The clinical safety and efficacy of SRP 4045 and SRP-4053 for the treatment of DMD patients is currently under evaluation but not yet known. Nonclinical studies of a surrogate exon-skipping PMO in a mouse model of DMD demonstrated exon skipping and beneficial effects on muscle strength and function. However, eteplirsen, a PMO designed to skip exon 51 of the human dystrophin gene, received accelerated approval in the US based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen (EXONDYS 51 Package Insert 2016). In addition, eteplirsen-treated patients (n = 12) evaluated over a 4-year period in the OL pivotal extension study (Study 4658-us-202) demonstrated a clinically relevant treatment benefit of 161 meters (p = 0.0007) on the 6-minute walk test (6MWT) and a lower incidence of loss of ambulation (16.7% vs. 76.9%) compared with untreated historical control patients (n = 13).

Accordingly, it is possible that treatment with SRP-4045 or SRP-4053 may confer benefit via production of dystrophin, which may ultimately lead to positive clinical effects on muscle function in patients amenable to exon 45 or exon 53 skipping, respectively. Such potential benefit would be available to the two-thirds of patients receiving active treatment during the double-blind placebo-controlled period of the study (up to 96 weeks), and to all patients who will receive active treatment during the 96-week OL extension.

In summary, the overall risk-benefit considerations for Study 4045-301 include the devastating and fatal nature of DMD, the paucity of therapeutic options and high unmet medical need, the absence of a limiting safety signal to date in clinical trials of SRP-4045 and SRP-4053, implementation of measures to mitigate potential risks associated with study procedures, and the potential benefit to patients receiving a possibly efficacious dystrophin-restoring therapy for 2 to 4 years.

6. STUDY OBJECTIVES

6.1. Double-Blind Study Period

6.1.1. Primary Objective

The primary objective of this study is to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) compared to placebo on ambulation, endurance, and muscle function, as measured by the 6MWT.

6.1.2. Secondary Objectives

The secondary objectives are to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on:

- Dystrophin protein expression in biopsied muscle tissue as measured by:
  - Western blot (quantification)
  - Immunohistochemistry (IHC) fiber intensity
- Functional status as measured by:
  - Ability to rise independently from the floor (without external support)
  - Loss of ambulation (LOA)
  - North Star Ambulatory Assessment (NSAA)
  - Respiratory muscle function as measured by forced vital capacity (FVC)% predicted
  - Frequency of falls
  - Cardiac function, as measured by left ventricular ejection fraction (LVEF)
- Safety and tolerability of SRP-4045 and SRP-4053.

6.1.3. Additional Efficacy Objectives

6.2. Open-Label Study Period

Objectives of the OL study period:

- Evaluate the long-term effects of SRP-4045 and SRP-4053 treatment on functional status up to 192 weeks.
- Evaluate the long-term safety and tolerability of SRP-4045 and SRP-4053.
- [redacted]

6.3. Pharmacokinetic Objective

The PK objective is to evaluate the PK properties of SRP-4045 and SRP-4053 via a population PK model.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a double-blind, placebo-controlled, multicenter study with an OL extension to evaluate the efficacy and safety of 2 PMOs, SRP-4045 and SRP-4053, in approximately 99 patients with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 and 53, respectively. A placebo group will be employed, and patients will be randomized [redacted] in a double-blind fashion in a 2:1 ratio, combined-active (SRP-4045 or SRP-4053) to placebo. [redacted].

Patients will be evaluated for inclusion during a Screening period of up to 8 weeks. Eligible patients who have out-of-frame deletions amenable to exon 45 or 53 skipping will be randomized in a 2:1 ratio between the active group and the placebo group to receive once weekly IV infusions of study treatment for up to 96 weeks. DMD patients amenable to exon 45 skipping will be randomized in a 2:1 ratio to receive either SRP-4045 or matching placebo, and DMD patients amenable to exon 53 skipping will be randomized in a 2:1 ratio to receive either SRP-4053 or matching placebo. Thus, SRP-4045 and SRP-4053 will each be administered as monotherapy only, and not coadministered. [redacted]

Efficacy, including the 6MWT, will be assessed at regularly scheduled study visits and safety will be monitored on an ongoing basis for all patients. Upon qualification for the study based on Screening and Baseline assessments and after eligibility is confirmed by both the local site and the Sponsor's Medical Monitor, all patients will undergo a muscle biopsy at Baseline. A second biopsy will be performed at Week 48. [redacted]

Safety will be assessed through the collection of adverse events, laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations throughout the study as described in Section 2.

[redacted]

An independent DMC will be formed to assist in the periodic monitoring of safety, data quality, and integrity of study conduct. In addition, the DMC will review the interim efficacy analysis performed when 75% of patients [redacted] have 6MWT data available at Week 48 in the double-blind period of the study, to determine whether the primary endpoint has been met and all patients may enter the OL period of the study and receive active

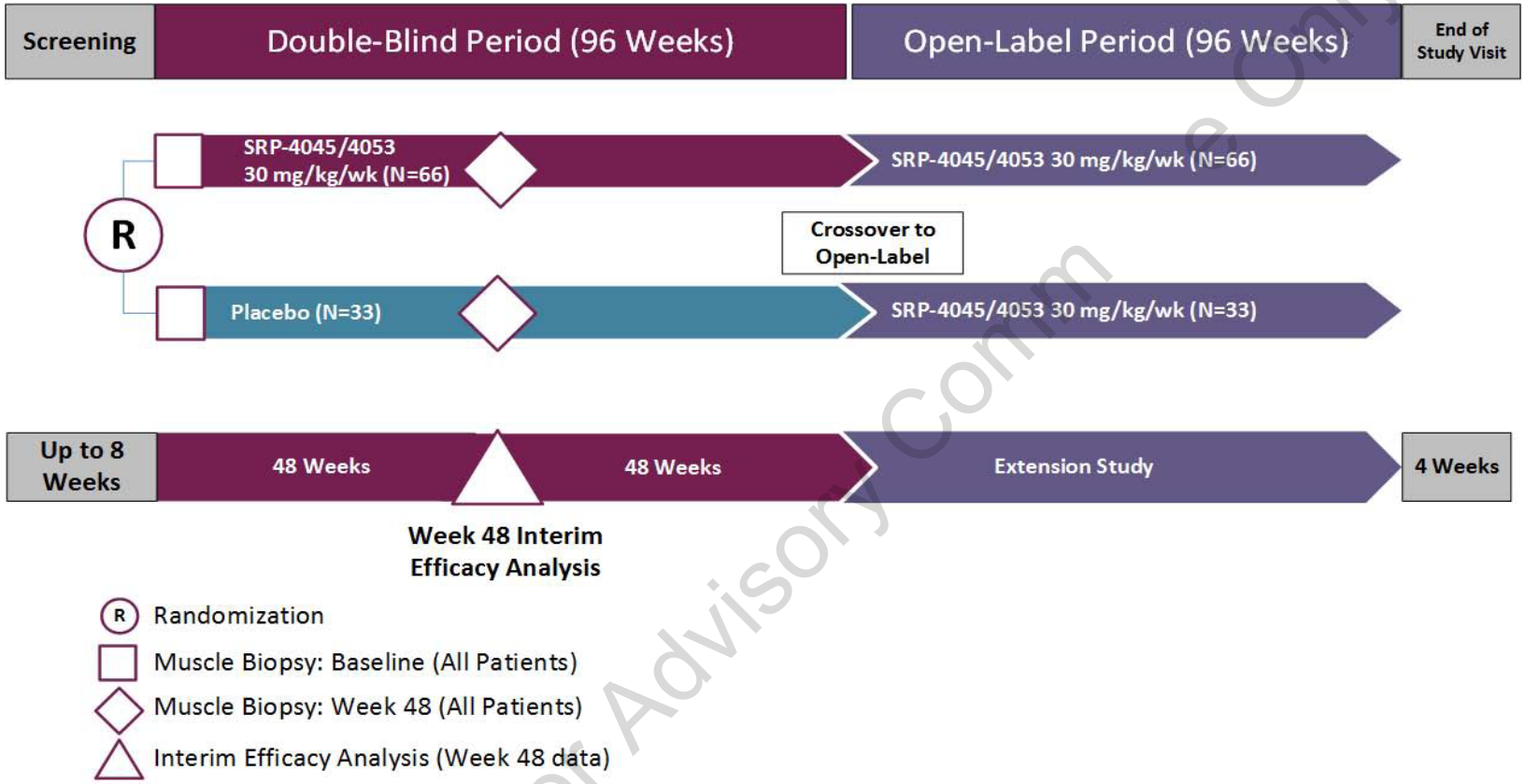
treatment, or whether patients must continue on double-blind placebo-controlled treatment through Week 96.

All patients may participate in the OL extension treatment period of the study for up to an additional 96 weeks, as described in the Schedule of Events (Section 2). Patients who received placebo in the double-blind treatment period of the study will receive OL active treatment via weekly infusions with either SRP-4045 or SRP-4053 according to their genotype. Efficacy, including the 6MWT, will be assessed at regularly scheduled study visits and safety will be monitored on an ongoing basis for all patients during the OL treatment period. [redacted] blood samples for assessing plasma drug concentrations will be obtained at select participating sites [redacted]

The total duration including the Screening/Baseline, Double-Blind Treatment, Open-Label Treatment, and Safety Follow-up periods is approximately 204 weeks.

Figure 1 is a schematic of the study design. Refer to Section 10 for the detailed list of study assessments.

Figure 1 Study Schematic for Study 4045-301



7.2. Dose Selection Rationale

The doses of SRP-4045 and SRP-4053 selected for use in this study are each 30 mg/kg. These doses were chosen based, in part, on results from studies with surrogate PMOs that have the same mechanism of action in animal models of DMD. Specifically, studies with AVI-4225 in the *mdx* mouse model demonstrated a clear dose-response relationship for PMO-induced dystrophin production and the data suggested that repeated (once weekly or biweekly) IV administration of human-targeted PMOs at doses in the range of 5 to 60 mg/kg could be effective in treating DMD (Malerba 2011, Wu 2011, Malerba 2009, Fletcher 2006). Eteplirsen is another PMO that shares with SRP-4053 and SRP-4045 the same chemical backbone, mechanism of action (exon skipping), disease mechanism targeted (absence of dystrophin protein due to an out-of-frame deletion within the DMD gene), and goal of de novo dystrophin production. Once-weekly IV infusions of eteplirsen at 30 mg/kg to DMD patients amenable to skipping exon 51 demonstrated the expected pharmacodynamic effect of exon 51 skipping and induced dystrophin expression. Accordingly, the 30-mg/kg dose of eteplirsen was approved by the Food and Drug Administration (FDA) for the treatment of DMD in patients who have a confirmed mutation in the *DMD* gene that is amenable to exon 51 skipping (EXONDYS 51 USPI). In Study 201/202, a higher dose of eteplirsen (50 mg/kg once weekly) was evaluated; however, the 50-mg/kg dose was not more effective than 30 mg/kg in restoring dystrophin expression in these patients.

[redacted]

In the Phase 1 studies of SRP-4053 and SRP-4045, PK analysis of samples obtained during dose titration have indicated that the plasma PK profiles of these PMOs are similar to that of eteplirsen. All 3 PMOs show dose proportionality in maximum plasma concentration (C_{max}) and AUC across the dose ranges studied for each molecule, between 4 and 30 mg/kg for SRP-4053 and SRP-4045, and between 0.5 and 50 mg/kg for eteplirsen. Plasma exposure (based on AUC) was greater with 30 mg/kg SRP-4053 and SRP-4045 than that achieved following the same dose of eteplirsen. Therefore, based on the clinical experience with eteplirsen, the 30 mg/kg dose of SRP-4053 or SRP-4045 in patients with DMD is expected to achieve relevant concentrations in the target tissues for exon skipping to occur. Plasma clearance was roughly similar across the 3 molecules and half-life was short, approximately 3 to 4 hours. The predominant pathway for elimination of drug for each of the 3 PMOs was via renal excretion, with approximately 60% of the dose excreted in urine within 24 hours. The vast majority of the dose was excreted within the first 4 hours. Because of the rapid clearance and short half-life, little to no accumulation was observed with weekly dosing.

[redacted]

[redacted]

In conclusion, the 30-mg/kg dose level for the human-targeted PMOs SRP-4053 and SRP-4045 has both nonclinical and clinical evidence for its selection as the appropriate dose for evaluating efficacy in Study 4045-301. Additional nonclinical and clinical data for SRP-4053 and SRP-4045 are described in the respective Investigator Brochures.

7.3. Study Endpoints

7.3.1. Efficacy Endpoints

7.3.1.1. Primary Efficacy Endpoints

The primary efficacy endpoints are:

[redacted]

- Change from Baseline at Week 96 in 6MWT

7.3.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Change from Baseline at Week 48 in the quantity of dystrophin protein expression as measured by Western blot of biopsied muscle tissue.
- Change from Baseline at Week 48 in the intensity of dystrophin expression in biopsied muscle tissue, as measured by IHC.
- Ability to rise independently from the floor (without external support) at Week 96 [redacted]
- Time to LOA from randomization through Week 96.
- Change from Baseline at Week 96 in:
  - NSAA total score
  - FVC% predicted
  - Frequency of falls
  - LVEF

7.3.1.3. Additional Efficacy Endpoints

[redacted]

7.3.2. Safety Endpoints

The safety and tolerability of SRP-4045 and SRP-4053 will be assessed through a review and evaluation of:

- AEs, SAEs, deaths, and discontinuations due to AEs
- Laboratory testing including hematology, coagulation, chemistry , and urinalysis
- Immunogenicity
- ECG
- Vital signs
- Physical examination findings

7.3.3. Pharmacokinetic Endpoints

Standard population PK parameters will be estimated by population PK analysis.

7.4. Discussion of Study Design

DMD is a rare, serious, debilitating, and ultimately fatal disease for which there is an urgent need to develop safe and effective therapies. In order to efficiently meet this urgency and the needs of the patient community, the study evaluates the effect of 2 active treatments, SRP-4045 or SRP-4053, compared to placebo treatment in patients with DMD mutations, which may be amenable to exon 45 or 53 skipping, respectively. Patients who are randomized to active treatment will be administered the appropriate active treatment for their respective genotype and analyzed as a single "combined-active group" in comparison to the placebo group.

The placebo-controlled design of the double-blind treatment period was chosen to reduce potential bias during data collection and evaluation of outcome parameters. The 96-week double-blind treatment duration of the study provides sufficient time to obtain safety and efficacy data, and the interim analysis at Week 48 will potentially minimize the duration of placebo treatment for patients in this study. A 96-week OL extension period has been added to

the study in which all patients will be assigned to either SRP-4045 or SRP-4053 administered as appropriate for their respective genotype to obtain long-term efficacy and safety data for the active treatments.

Because the kidney has been identified as the main target organ for toxicity in nonclinical studies with SRP-4053 and SRP-4045, the Sponsor has identified renal toxicity as a safety topic of interest. Therefore, renal function will be closely monitored during this study via clinical laboratory testing (see Section 2 for the testing schedule and Section 10.4.3 for a complete list of tests).

7.5. Data Monitoring Committee

An independent DMC will be formed to assist in the periodic monitoring of safety, data quality, and integrity of study conduct, as well as to evaluate an interim analysis of efficacy data once 75% of patients [redacted] have Week 48 6MWT data. This interim analysis is intended for the protection of patients in order to minimize the duration of placebo exposure if there is early and overwhelming evidence of efficacy. The first DMC meeting is planned to be held 6 months after treatment initiation for the first patient in the study and approximately every 6 months thereafter throughout the study. At each DMC meeting, the DMC will review the cumulative safety data and make one of the following recommendations: study may proceed as planned, resume study with major/minor modifications (to be specified), temporarily suspend enrollment and/or dosing pending further DMC evaluation, or permanently discontinue the study.

The interim analysis of efficacy will be performed when Week 48 6MWT data are available for 75% of patients [redacted]. If efficacy is clearly demonstrated on 6MWT and safety results are acceptable, the DMC will recommend stopping the double-blind placebo-controlled period early and start OL treatment for all patients. If the interim analysis does not meet the required criteria, the DMC will recommend continuing the double-blind placebo-controlled study period to Week 96.

Any decision to interrupt, restart, or discontinue the study will be made by the Sponsor in consultation with the DMC and other parties, as appropriate.

A DMC charter will be prepared to formalize the process for the meetings and data reviews. The outcome of any DMC meeting will be communicated to the Investigators by the Sponsor or designee. The relevant regulatory authorities will be promptly notified of study suspension or discontinuation related to safety concerns. Any suspension or discontinuation of the study for any reason will be promptly reported to the relevant Institutional Review Board/Independent Ethics Committee (IRB/IEC).

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Number of Patients

Approximately 99 patients will be included in this study in a first-come, first-to-be-enrolled fashion. Approximately 66 patients will be randomized to the combined-active group (SRP-4045 or SRP-4053) and approximately 33 patients will be randomized to the placebo group. [redacted]

8.2. Patient Inclusion Criteria

A patient must meet all of the following criteria to be eligible for this study.

1. Is a male with an established clinical diagnosis of DMD and an out-of-frame deletion amenable to:
   - Exon 45 skipping [redacted] OR
   - Exon 53 skipping [redacted]

   [redacted] The patient's amenability to exon 45 or 53 skipping must be confirmed prior to first dose using the genotyping results obtained during Screening.
2. Is between 7 and 13 years of age, inclusive, at randomization.
3. Has stable pulmonary function (FVC% of predicted ≥50% and no requirement for nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Has intact right and left biceps brachii muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Has been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks [redacted]
6. [redacted]
7. Achieved a mean 6MWT distance of ≥300 to ≤450 meters [redacted]

8. 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 (eg, male condom or female oral contraceptives) during this time frame.
9. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.
10. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the patient to participate in the study.

8.3. Patient Exclusion Criteria

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

1. Treatment with any of the following investigational therapies according to the time frames specified:
   - [redacted]
   - Utrophin upregulating agents (eg, ezutromid [SMT C1100] or other)
   - [redacted]
   - PRO045 (BMN 045)
   - PRO053 (BMN 053)
   - [redacted]

- For any experimental treatment not otherwise specified in Exclusion Criterion 1, consult the medical monitor.

2. Treatment with any of the following non-investigational therapies according to the time frames specified:

[redacted]

3. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable.
4. Presence of any other significant genetic disease other than DMD (eg, dwarfism).
5. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
6. LVEF <50% on the Screening echocardiogram (ECHO) [redacted].
7. [redacted]
8. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, patients who seem unable/unwilling to comply with the study procedures, in the Investigator's opinion, are to be excluded.

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

The length of a patient's participation will be from the time the informed consent form is signed until completion of the End of Study (Week OL100) visit (up to 204 weeks).

8.5. Patient Withdrawal Criteria

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

Investigator may also stop the study participation of any patient at any time. Reasons for study withdrawal include but are not limited to:

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

The Investigator or study staff will document the reason(s) for treatment discontinuation on the case report form (CRF).

[redacted]

Patients withdrawn from treatment will not be replaced.

8.6. Study Discontinuation

If the Sponsor, the Investigator, the medical monitor, the study monitor, the DMC, IRB/IEC, and/or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among (at a minimum) the Sponsor, the Investigator, 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 investigational product (IP)
- 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 21 CFR 312 or the European Clinical Trial Directive 2001/20/EC
- Study termination and follow-up will be performed in compliance with the conditions set forth in International Conference on Harmonisation (ICH) E6 on Good Clinical Practice (GCP) as well as 21 CFR 312.56b and the European Clinical Trial Directive 2001/20/EC which require a Sponsor to ensure an Investigator's compliance with these requirements and to promptly secure a plan for compliance or discontinue shipments of the IP to the Investigator and end the Investigator's participation in the study.

9. TREATMENT OF PATIENTS

9.1. Investigational Products

The IPs (SRP-4045 Injection and SRP-4053 Injection) are supplied as concentrated sterile solutions, which are diluted with 0.9% sodium chloride injection prior to administration via an IV infusion.

SRP-4045 Injection and SRP-4053 Injection are sterile, clear, colorless, isotonic, phosphate-buffered saline (PBS) solutions supplied in single-use 2-mL glass vials containing 2 mL of SRP-4045 or SRP-4053 at a concentration of 50 mg/mL.

Matching Placebo Injection (PBS) is identical to SRP-4045 Injection and SRP-4053 Injection, except without the active ingredient.

9.1.1. Packaging and Labeling

Please refer to the study-specific Pharmacy Manual for information on packaging and labeling. Packaging and labeling for SRP-4045, SRP-4053, and matching Placebo Injection are identical in appearance (ie, vial label text: “SRP-4045 or Placebo”; “SRP-4053 or Placebo”).

The label text for the study treatments will comply with applicable regional, national, and local laws and regulations and will include at a minimum the protocol number, contents of the vial, the appropriate regional cautionary statements, lot number, storage conditions, and the name of the Sponsor (Sarepta Therapeutics, Inc.).

9.1.2. Storage

Store the study treatment at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store in the original carton until ready for use.

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

9.2. Treatments Administered

In the double-blind treatment period, eligible patients will be randomized to receive a weekly IV infusion of study treatment (30 mg/kg of SRP-4045 or SRP-4053, according to genotype, or placebo) for up to 96 weeks, or for a shorter duration if the primary efficacy endpoint has been met early based on DMC review of the Week 48 interim analysis of 6MWT data (see Section 7.5 and Section 13.11 for details of the interim analysis). After completion of double-blind placebo-controlled treatment, patients may cross over to receive OL active treatment (30 mg/kg of SRP-4045 or SRP-4053, according to genotype) for up to 96 weeks beginning at Week OL1.

The dose of SRP-4045 or SRP-4053 will be calculated based on patient weight. [redacted]

Dosing calculations for blinded preparation of infusions (including placebo) will be based on a

dose of 30 mg/kg. Infusion solutions of SRP-4045 or SRP-4053 are to be prepared by following the steps detailed in the study-specific Pharmacy Manual.

Study treatment will be administered as an IV infusion over a period of approximately 35 to 60 minutes. It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream, or other per the Investigator's discretion) be applied to the infusion site prior to each administration of study treatment. Additional administration and IP details are available in the study-specific Pharmacy Manual.

In the US, implantable central venous catheters are precluded from use in this study during the double-blind, placebo-controlled treatment period but are permitted for use during the OL period, during which all patients will be receiving active treatment. In other countries, in the event it becomes necessary, venous access methods such as midline catheter, central line, or portacath may be used for study infusions at the Investigator's discretion, contingent upon country-specific regulatory approval of the method to be used.

~~In the US, implantable central venous catheters are precluded from use in this study during the double-blind, placebo-controlled treatment period but are permitted for use during the OL period, during which all patients will be receiving active treatment. In other countries, I~~in the event it becomes necessary, venous access methods such as midline catheter, central line, or portacath may be used ~~for study infusions~~ at the Investigator's discretion, contingent upon ~~country-specific regulatory~~ approval by local and/or country-specific regulatory body(ies) ~~of the method to be used~~.

If study treatment is administered into an existing IV line, the line must be flushed with normal saline before and after administration of study treatment. No other medications may be administered concomitantly during the study treatment infusion.

All patients will be observed for at least 1 hour following the end of each infusion.

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

1. Patients should receive study treatment once every 7 days starting at the Week 1 visit. [redacted]
2. [redacted]
3. [redacted]

9.2.1. Dose Modification, Reduction, or Delay

There is no provision for dose alteration in this study. [redacted]

9.3. Randomization and Blinding

9.3.1. Randomization

A total of approximately 99 eligible patients will be randomized. Randomization will be carried out separately for each of the 2 genotypes (SRP-4045 or SRP-4053) using a 2:1 ratio between the active group and the placebo group. [redacted] Randomization will be performed at Baseline using an interactive voice response (IVR) system.

9.3.2. Blinding for Dose Administration

In the double-blind, placebo-controlled treatment period of the study, all patients, parents/guardians, Investigators, pharmacist(s) performing drug preparation, and site staff will be blinded to treatment assignment.

9.3.3. Blinding for Clinical Evaluators

To minimize assessment bias, clinical evaluators will be trained on how to maintain blinding to treatment as best as possible. In order to maintain the study blind, interaction between parents and clinical evaluators should be minimized.

9.3.4. Blinding for Laboratory Assessments

Biopsy samples will undergo initial processing at a central histology laboratory, at which time any unblinding headers such as dates, visits, and subject numbers will be masked. Blinding will be maintained with regard to treatment group and biopsy time point.

A detailed description of these procedures can be found in the Laboratory Manual.

9.3.5. Unblinding Procedures

In the event of a medical emergency wherein the knowledge of the subject's treatment assignment may influence clinical decision-making, the Investigator has the option to unblind treatment assignment using the IVR system. Please see Section 11.7.4 for additional information regarding unblinding in emergency situations.

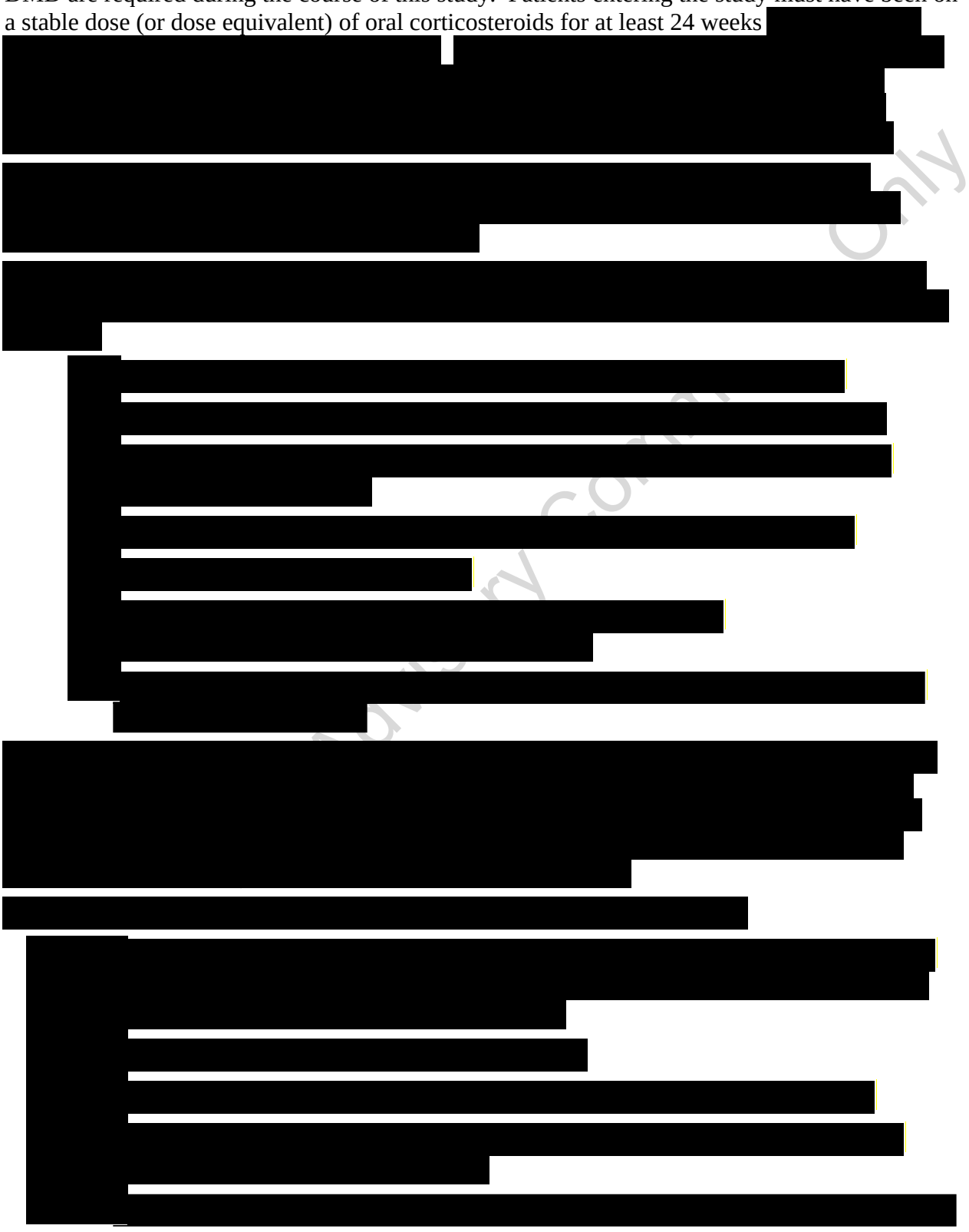
[redacted]

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

9.4. Prior and Concomitant Medications

Patients are not permitted to participate in another interventional clinical trial while enrolled in this study. If the Investigator is unsure of the impact of a concomitant medication on study assessments and outcomes, then he/she should contact the Medical Monitor.

Oral corticosteroids, including but not limited to prednisolone and prednisone, for treatment of DMD are required during the course of this study. Patients entering the study must have been on a stable dose (or dose equivalent) of oral corticosteroids for at least 24 weeks [redacted]



9.5. Treatment Compliance

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

10. STUDY ASSESSMENTS

10.1. Study Schedule of Events

The schedule outlining the study assessments and times of assessments is shown in Section 2. Written informed consent from the parent(s)/legal guardian(s) and assent from the patient (if applicable) to participate in this study must be obtained prior to beginning any of the procedures for this study.

10.2. Study Assessments by Visit

Assessments of adverse events, concomitant medications and therapies, and physiotherapeutic interventions will be performed at every study visit. [redacted]

[redacted]

10.2.1. Screening Period (Up to [redacted] weeks prior to Week 1)

[redacted]

- Screening Informed Consent and Assent, if applicable – [redacted]
- Assess inclusion and exclusion criteria for eligibility
- Medical history, including treatment history
- Full physical examination, including examination of general appearance; head, eyes, ears, nose, and throat (HEENT); heart; chest; abdomen; skin, lymph nodes; extremities; musculoskeletal; and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Collection of a blood sample to confirm genotype and biomarkers [redacted] Confirmation of *DMD* genotyping is required for

determination of patient eligibility.

- Height

(Screening Functional Assessment Visit):

- Informed Consent and Assent, if applicable–

10.2.2. Baseline Period

(Baseline Functional Assessment Visit;

[redacted]

- Assess inclusion and exclusion criteria and confirm eligibility
- Vital signs
- Weight
- Height

[redacted]

(After eligibility has been confirmed)

The muscle biopsy is performed as the last Baseline procedure

Informed Consent and Assent, if applicable–

- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Blood sample for biomarkers of DMD disease progression

10.2.3. Double-Blind Treatment Period: Procedures for Weeks 1 to 96

- All safety laboratory assessments (chemistry, hematology, coagulation, and urinalysis) will be collected weekly at Weeks 1 through 8 inclusive, and every 12 weeks thereafter beginning at Week 12 and continuing through Week 96 inclusive (Weeks 12, 24, 36, 48, 60, 72, 84, and 96).
- Vital signs, including include blood pressure, heart rate, respiration, and oral temperature.
- Blinded study treatment will be administered once weekly via IV infusion, as described in Section 9.2. Refer to the Pharmacy Manual for specific instructions regarding preparation of the study treatment for infusion.

10.2.3.1. Additional Procedures for Week [redacted]

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight (this measurement will be used to calculate the first study treatment dose until the next study weight is obtained)
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis.
- Blood sample for immunogenicity assessment
- Blood sample for biomarkers of DMD disease progression
- [redacted] Blood samples for assessing plasma drug concentrations (PK) will be obtained [redacted]

10.2.3.2. Additional Procedures for Week [redacted]

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Blood sample for biomarkers of DMD disease progression

10.2.3.3. Additional Procedures for Week [redacted]

[redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment

[redacted] Blood samples for assessing plasma drug concentrations (PK) will be obtained [redacted]

10.2.3.4. Additional Procedures for [redacted] (Functional Assessment Visits)

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment

[redacted]

[redacted]

10.2.3.5. Additional Procedures for Weeks [redacted]

[redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight
- Blood samples for assessing plasma drug concentrations (PK) will be obtained [redacted]

10.2.3.6. Additional Procedures for Weeks [redacted]

[redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight

10.2.3.7. Additional Procedures for Week [redacted] (Functional Assessment Visit)

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Blood samples for assessing plasma drug concentrations (PK) will be obtained

10.2.3.8. Additional Procedures for Week [redacted] (Functional Assessment Visit)

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Blood samples for assessing plasma drug concentrations (PK) will be obtained

[redacted]

[redacted]

- All patients will have a muscle biopsy performed following the Week 48 infusion [redacted]

10.2.3.9. Additional Procedures for Weeks [redacted] (Functional Assessment Visits)

[redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis

[redacted]

[redacted]

10.2.3.10. Additional Procedures for Weeks [redacted] (Functional Assessment Visits)

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Blood samples for assessing plasma drug concentrations (PK) will be obtained

[redacted]

10.2.4. Open-Label Treatment Period: Procedures for Weeks OL1 to OL96 Inclusive

An OL treatment period of up to 96 additional weeks will commence at Week OL1 after the end of the 96-week double-blind treatment period, or after the DMC has reviewed the Week 48 interim analysis and determined that the primary endpoint has been met and all patients may cross over to OL active treatment.

The assessments for the OL treatment period are described in the Schedule of Events (Table 3).

- Before patients may begin OL treatment, safety laboratory assessments must be performed within 2 weeks prior to the first dose. Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.
- All safety laboratory assessments will be collected at Weeks

- Unblinded study treatment will be administered once weekly via IV infusion, as described in Section 9.2. [redacted] Refer to the Pharmacy Manual for specific instructions regarding preparation of the study treatment for infusion.

10.2.4.1. Additional Procedures for Week [redacted]

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis

10.2.4.2. Additional Procedures for Week [redacted]

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis

10.2.4.3. Additional Procedures for Week [redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment

10.2.4.4. Additional Procedures for Weeks [redacted] (Functional Assessment Visits)

[redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis

[redacted]

10.2.4.5. Additional Procedures for Weeks [redacted] (Functional Assessment Visits)

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Blood samples for assessing plasma drug concentrations (PK) will be obtained

[redacted]

10.2.4.6. Additional Procedures for Week [redacted] (Functional Assessment Visit)

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Blood samples for assessing plasma drug concentrations (PK) will be obtained

[redacted]

[redacted]

10.2.4.7. Additional Procedures for Weeks [redacted]

[redacted]

- Brief physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, and skin
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis

10.2.4.8. Additional Procedures for Week [redacted] (or Early Termination Visit [redacted]

[redacted]

- Full physical examination, including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight

[redacted]

- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment
- Serum sample for biomarkers of DMD disease progression
- Blood samples for assessing plasma drug concentrations (PK) will be obtained

10.2.5. Procedures for Week [redacted] (End of Study Visit or Approximately [redacted] Days after Early Termination Visit)

Assessments should occur during a single day at the patient's [redacted] Site.

- Full physical examination including examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems
- Vital signs
- Weight
- Safety laboratory assessments, including chemistry, hematology, coagulation, and urinalysis
- Blood sample for immunogenicity assessment

10.3. Efficacy Assessments

10.3.1. Primary Efficacy Assessment: 6-Minute Walk Test

The 6MWT will be performed by standardized procedures for patients as outlined in Section 2 and in the Clinical Evaluator Manual. [redacted]

10.3.2. Secondary Efficacy Assessments

10.3.2.1. Muscle Biopsy

Upon qualification for the study based on Screening and Baseline assessments and after eligibility is confirmed by the Sponsor, all patients will undergo a muscle biopsy at Baseline. A second biopsy will be performed at Week 48. [redacted]

[redacted]

10.3.2.2. Pulmonary Function Tests (PFTs)

PFTs will be performed [redacted] at the time points specified in the Schedule of Events (Section 2), depending on the study visit and using standard spirometry procedures. [redacted]

10.4. Safety Assessments

10.4.1. Physical Examination

Physical examinations, full and brief, will be conducted at the time points specified in Section 2. Physical examinations will be performed by the Investigator or qualified study staff. Full physical examinations will include examination of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems. Brief physical examinations will include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

[redacted]

10.4.2. Vital Signs, Weight, and Height

Vital signs (blood pressure, heart rate, respiration, and oral temperature), height, and weight will be measured at the time points specified in Section 2.

[redacted]

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

Weight is to be recorded in kilograms. [redacted]

10.4.3. Clinical Laboratory Evaluations

The following routine clinical laboratory tests will be performed at the time points specified in Section 2. Samples will be collected and processed according to the Laboratory Manual provided for the study and analyzed by an accredited central laboratory selected by the Sponsor:

Chemistry: [redacted]

Hematology: [redacted]

Coagulation Screen: [redacted]

Urinalysis: [redacted]

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 (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in assessment results that has medical relevance resulting in an alteration

in medical care. If clinically significant deterioration from Baseline levels is noted, the Investigator will continue to monitor the patient with additional assessments until:

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

10.4.4. Electrocardiogram

Twelve-lead ECGs will be obtained at the time points specified in Section 2. ECGs will be performed at a consistent time of day throughout the study. ECGs will be performed only after the patient is in the supine position, resting, and quiet for a minimum of 15 minutes. The ECG will be manually reviewed and interpreted by medically qualified personnel using a central vendor according to prespecified criteria. [redacted]

10.4.5. Concomitant Medications and Therapies

Concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be reviewed and recorded at each visit from the time the parent(s)/guardian(s) sign(s) the informed consent and the patient signs the assent form (if applicable). Information on any physiotherapeutic intervention must be collected in detail for this study.

10.4.6. Adverse Events

The collection of AEs is described in Section 11.

10.4.7. Immunogenicity Assessment

Blood serum samples will be collected at the time points specified in Section 2 to determine the development of immunogenicity over the course of the study.

10.5. Additional Assessments

Details about how additional assessments are performed are provided in the Clinical Evaluator Manual.

10.5.1. North Star Ambulatory Assessment (NSAA)

The NSAA will be performed [redacted] at the time points specified in Section 2, [redacted] The NSAA is a clinician-administered scale that rates patient performance on various functional activities (Mazzone 2010). [redacted]

[redacted]

10.5.7. Echocardiogram

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in Section 2. ECHOs will be performed at a consistent time of day throughout the study. [redacted] The Investigator will review the results of the ECHO report and determine if the findings are clinically significant.

[redacted]

10.5.9. Potential Disease-Related Biomarkers

Blood samples for exploratory analyses to identify and evaluate potential disease-related biomarkers in serum will be obtained as outlined in the Schedule of Events, where local regulations and blood volume limitations permit.

[redacted]

Collection of samples for potential disease-related biomarker analysis will be subject to discretionary approval from each center's IRB/IEC and the specific written consent of the patient and/or the patient's parent or legal guardian. This section of the protocol only applies if approval for collection of these additional samples has been granted by the IRB/IEC and consent is provided by the patient (or the patient's parent or legal guardian).

Samples will be stored by the Sponsor or designee in a secure and controlled environment until analysis, and will be destroyed by the Sponsor or designee after all worldwide obligations have been met, or sooner if required by local regulations.

Refer to the Laboratory Manual for further details regarding the collection, processing, and storage of these samples.

[redacted]

10.6. Pharmacokinetic Assessments

During the double-blind study period, blood samples for assessing plasma drug concentrations will be obtained at Weeks [redacted]

[redacted]

In the OL study period, blood samples for assessing plasma drug concentrations will be obtained at Weeks [redacted]

Refer to the Laboratory Manual for the study for sample processing. Plasma samples will be analyzed to determine concentrations of SRP-4045 and SRP-4053.

11. ADVERSE EVENTS

11.1. Collection of Adverse Events

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

All AEs from the time of informed consent/assent through the last follow-up visit will be recorded in each enrolled patient's CRF. For patients who prematurely discontinue from the study (see Section 8.5), AEs will continue to be recorded until 28 days after the last study treatment infusion. For patients who are found to be ineligible for the study during the Screening period and are not enrolled (ie, Screening failures), only SAEs (Section 11.2.2) will be reported (Section 11.6).

If, at any time after the patient has completed participation in the study (see Section 8.5), the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly/probably or definitely related to the IP (Section 11.4.1) or is possibly/probably or definitely related to a study procedure (Section 11.4.2), then the event and any known details must be reported promptly to the Sponsor.

11.2. Definition of Adverse Events

11.2.1. Adverse Event (AE)

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

Adverse events include:

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

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

11.2.2. Serious Adverse Event (SAE)

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, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.

- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected due protocol procedures, based on Investigator judgment, will be considered prolonged hospitalizations.
- **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 IP.
- **Important medical events**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.3. Clinical Laboratory Abnormalities

Any laboratory abnormality deemed clinically significant by the Investigator should be recorded as an AE. A clinically significant abnormality is 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. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis (e.g., anemia) should be recorded as the AE term. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

11.4. Classification of Adverse Events

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

11.4.1. Relationship to Investigational Product

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

Unrelated:	The event is clearly not related to the study treatment
Possibly/probably related:	The event could be related/is likely to be related to the study treatment
Definitely related:	The event is clearly related to the study treatment

11.4.2. 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:	The event is clearly not related to the study procedures
Possibly/probably related:	The event could be related/is likely to be related to study procedures
Definitely related:	The event is clearly related to the study procedures

11.4.3. 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:	The event is clearly not related to the underlying disease
Possibly/probably related:	The event could be related/is likely to be related to the underlying disease
Definitely related:	The event is clearly related to the underlying disease

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

11.4.4. Severity of Adverse Events

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

The Investigator will assess the severity of all AEs as Mild, Moderate, or Severe, based on the following definitions:

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

11.4.5. Outcome

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

11.4.6. Action Taken Regarding the Investigational Drug Product

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

11.4.7. Expectedness of an Adverse Event

The expectedness of all AEs will be determined according to the most recent versions of the Investigator's Brochures for SRP-4045 and SRP-4053.

11.4.8. Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected unexpected serious adverse reactions (SUSARs) will be handled by appropriate Sponsor or designee personnel and reported within the required timelines in an unblinded fashion to regulatory authorities and IRB/IEC per the requirements of the concerned competent authorities. SUSARs will also be reported in a blinded fashion to study Investigators. Investigators may request SUSARs to be unblinded.

11.5. Recording Adverse Events

All AEs from the time of informed consent/assent through the last follow-up visit will be recorded in each enrolled patient's CRF. For patients who prematurely discontinue from the study (see Section 8.5), AEs will continue to be recorded until 28 days after the last study treatment infusion. For patients who are found to be ineligible for the study during the Screening period and are not enrolled (ie, Screening failures), only SAEs (Section 11.2.2) will be reported (Section 11.6).

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

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

11.6. Reporting Serious Adverse Events

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

11.7. Special Situations

11.7.1. Pregnancy

If the female partner of a treated male subject becomes pregnant, the male subject must notify the Investigator within 24 hours of learning of the pregnancy. The Investigator must make every effort to ensure that the pregnant female is aware of the need to notify her healthcare provider regarding her male partner's participation in this clinical trial and his potential exposure to SRP-4045 or SRP-4053.

The study site must complete a pregnancy form and send to the Sponsor or designee within 24 hours of learning of the pregnancy. The study site will make every effort to follow the pregnancy till outcome is known.

11.7.2. Overdose

Currently, there is no basis for determining a clinically meaningful definition of overdose for SRP-4053 or SRP-4045. [redacted]

An overdose is not an AE. An overdose will be reported even if it does not result in an AE. An overdose will be recorded on the appropriate form and sent to the Sponsor or designee within 24 hours.

11.7.3. Death

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

11.7.4. Unblinding due to a Medical Emergency

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

The reasons for unblinding must be noted in the source documentation. The Investigator must not disclose information about treatment assignment to anyone who does not need the information due to their direct involvement in patient care. Disposition of patients who become unblinded due to medical emergency will be determined following discussion with the Sponsor.

11.7.5. Responsibilities of the Investigator

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

- Monitor and record all AEs
- Determine seriousness, severity, and relationship to IP and/or study procedure and/or underlying disease
- Determination of the onset and end date of each event

- Provide initial report on all SAEs within 24 hours of first knowledge to the Sponsor or designee
- Provide follow-up information on SAEs in a timely and proactive manner
- Respond to queries regarding AEs and SAEs in a timely manner
- Ensure source documentation for all AEs are accurate and complete
- Ensure that the study is conducted as defined in this document

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

11.7.6. Responsibilities of the Sponsor

The responsibilities of the study Sponsor (Sarepta Therapeutics, Inc.) include but are not limited to the following:

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

12. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

12.1. Recording of Data

Clinical data for this study will be captured in an electronic format. Electronic data capture (EDC) will be provided by a contract research organization (CRO). The Investigator, or personnel delegated by the Investigator, will perform primary data collection/perform assessments based on the protocol design and captured in source documentation. All required study information must be recorded on the appropriate CRF screens/forms using the CRF Completion Guidelines for the study. A CRF must be completed for each patient that is enrolled.

[redacted]

All data must be carefully entered in a timely fashion to permit meaningful interpretation and study oversight.

12.2. Quality Assurance

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

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by IRBs/IECs or regulatory authorities before, during, or after the study. The Investigator will allow and assist the Sponsor's representatives and any regulatory agency to have direct access to all study records, CRFs, 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 such as the US FDA.

12.3. Retention of Study Documents

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

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

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

If off-site 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

13.1. General Considerations

This section describes the rules, conventions, statistical analysis, and presentation of data for this study. Full details will be provided in the statistical analysis plan (SAP) for this study.

Revisions during the study may be made to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. If necessary and appropriate, revisions will be based on blinded review of the data. A formal SAP for the analysis and presentation of data from this study will be prepared and issued before database lock. The SAP will provide a more technical and detailed description of the proposed data analysis methods and procedures. Deviations from the statistical analyses outlined in this protocol will be included in this plan; any further modifications will be noted in the clinical study report (CSR). All statistical analyses will be performed under oversight of the Sponsor.

All available data will be included in data listings and tabulations. [redacted]

All data collected in this study will be presented using summary tables and patient data listings. Summary statistics for raw and change from Baseline data of continuous variables will minimally include n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Endpoints will be assessed using simple descriptive statistics and/or inferential statistics. [redacted]

13.2. Sample Size

[redacted]

13.3. Analysis Sets

Three analysis sets will be considered:

Intent-to-Treat (ITT) Analysis Set: The ITT analysis set will consist of all randomized patients with treatment group designated according to the randomization treatment assignment.

Safety Analysis Set: All patients who are randomized in the study and receive at least 1 dose of study treatment (SRP-4045, SRP-4053, or placebo), with treatment group designated according to actual treatment received.

Pharmacokinetic Analysis Set: Patients at selected sites who receive a full dose of study treatment [redacted], and for whom there are adequate PK samples from which to estimate population PK parameters.

13.4. Protocol Deviations

A listing of protocol deviations will be provided. This deviation listing will be based on blinded review of study data prior to locking the database and will include the nature of the deviation (e.g., inclusion/exclusion, prohibited therapies).

13.5. Disposition, Demographics, and Baseline Characteristics

The number and percentage of patients completing or prematurely discontinuing the study will be summarized. Age will be summarized both as a continuous variable [redacted]. Reasons for premature discontinuation will also be summarized.

Demographic characteristics including age (years), race, ethnicity, and Baseline characteristics including height (cm), weight (kg), body mass index (kg/m^2), [redacted] and 6MWT will be summarized. Demographic data and Baseline characteristics will be presented in data listings.

13.6. Medical History

Medical history will be presented in data listings.

13.7. Dosing and Compliance

The cumulative exposure to study treatment, including the total volume of drug administered (mL), total number of infusions received, and the cumulative amount of drug received, will be summarized by treatment group. Dosing information will be provided in a data listing.

13.8. Efficacy Analysis

The primary analyses of the efficacy endpoints will be performed on the ITT analysis set. All efficacy endpoints will be summarized descriptively by visit, if appropriate.

13.8.1. Analyses of the Primary Efficacy Endpoints

At the interim analysis, the primary efficacy endpoint will be the change from Baseline at Week 48 in 6MWT. At the final analysis, the primary efficacy endpoint will be the change from Baseline at Week 96 in 6MWT.

[redacted]

[redacted]

The primary analysis described above will be based on all patients in the ITT analysis set, including those with post-baseline missing values. [redacted]

13.8.2. Analyses of the Secondary Efficacy Endpoints

[redacted]

13.8.3. Analyses of Additional Efficacy Endpoints

The details of analyses of the additional efficacy endpoints will be specified in the SAP.

13.9. Safety Analysis

Safety analyses will be descriptive in nature. All safety data will be presented in the data listings.

13.9.1. Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group. Non-emergent events will be recorded in data listings. For all AE tables, the number and percent of patients reporting AEs will be grouped by SOC and PT. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

Multiple occurrences of the same AE at the PT (or SOC) level in the same patient will be counted only once in the calculation of the number and percent of patients reporting AEs for each PT (or SOC). If a patient experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship to study treatment and maximum severity will be used to summarize AEs by relationship and severity. Treatment-related TEAEs will be defined as those that the Investigator considers possibly/probably or definitely related to the study treatment.

The following summary tables will be produced:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- SAEs
- Deaths

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

The following listings will be produced:

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

13.9.2. Physical Examination, Vital Signs, Weight, and Height

Vital signs, weight, and height will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics. Frequency tables of predefined abnormal changes in vital sign values will be generated.

Results from physical examinations will be presented in patient data listings.

13.9.3. Clinical Laboratory Tests

Clinical chemistry, hematology, coagulation, and urinalysis will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics for each continuous parameter, and frequency tables for each discrete parameter. Frequency tables of predefined abnormal changes in select laboratory parameter values will be generated.

13.9.4. Immunogenicity

Results of immunogenicity assessments will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics.

13.9.5. Electrocardiograms

The actual value and change from Baseline to each visit will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics. Shift and frequency tables of predefined abnormal changes in select ECG parameter values will be generated.

13.9.6. Prior and Concomitant Medications and Physiotherapeutic Interventions

All prior and concomitant medications, as well as physiotherapeutic interventions, will be presented in data listings.

13.10. Pharmacokinetic Analysis

Individual plasma levels of SRP-4045 and SRP-4053 will be listed with the corresponding time related to study treatment administration, and summary statistics will be generated by per-protocol time of collection.

Population PK analysis of plasma concentration-time data of SRP-4045 and SRP-4053 will be performed [redacted]. Data may be combined with those of completed studies to support a relevant structural model. [redacted]

Population PK analysis will be presented in a separate technical document.

13.11. Interim Analysis

An interim analysis of efficacy will be performed when Week 48 6MWT data are available for 75% of the patients [redacted]

[redacted]

13.12. Other Statistical Issues

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

14. SPECIAL REQUIREMENTS AND PROCEDURES

14.1. Compliance with Ethical and Regulatory Guidelines

This study will comply with the requirements that are enunciated in the European Clinical Trial Directive 2001/20/EC and in the US Code of Federal Regulations (CFR).

14.2. Institutional and Ethics Review

This study will be conducted in full compliance with the IRB regulations in 21 CFR 56 and/or the European Clinical Trial Directive 2001/20/EC. Before enrollment of patients into the study, the protocol and informed assent (for patients, if applicable) and informed consent (for parents/legal guardians) documents will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol will be subjected to the same IRB/IEC and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the IP during the study. IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB/IEC and the regulatory authority must be retained in the study regulatory files.

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

Written informed consent from each patient's parent(s) or legal guardian(s) and written 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. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in the 21 CFR 50.25.

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 that are deemed by the Investigator as crucial for the safety and wellbeing of that patient may be instituted for that patient only and documented as deviations. The Investigator will contact the medical monitor as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB/IEC; however, the IRB/IEC and Medical Monitor must be notified in writing as soon as possible in accordance with the IRB/IEC policies after the departure has been made.

14.5. Confidentiality

14.5.1. Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, 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 Health Insurance Portability and Accountability Act (HIPAA) standards and/or European standards.

14.5.2. Patient Confidentiality

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

15. STUDY DOCUMENTATION AND GENERAL INFORMATION

15.1. Essential Study Documents

Essential study documents are among the critical documents required before study enrollment is to occur. Essential documents, as well as supplemental information such as the Investigator's Brochure, Pharmacy Manual, CRF Completion Guidelines, final protocol, as specified in the Clinical Operations Manual and/or Regulatory Binder, must be kept on-site in a designated study site file.

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

15.2. General Information

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

15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics, Inc. 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. Sarepta Therapeutics, Inc. will publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by Sarepta Therapeutics, Inc., as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov. After completion of the study, results will be disseminated through ClinicalTrials.gov.

15.4. 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 CRO.

16. LIST OF REFERENCES

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