CLINICAL STUDY PROTOCOL

DRUG (RESEARCH NO.):	SRP-4053
PROTOCOL NUMBER:	4053-101
PROTOCOL TITLE:	A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping
EUDRACT NUMBER:	2014-002008-25
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION (DATE):	08 November 2017 (Amendment 8)
REPLACES VERSION (DATE):	21 April 2017 (Amendment 7)

[redacted]

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping
Study No:	4053-101 (Version 9; Amendment 8)
Current Version (Date):	08 November 2017

This study protocol was subject to detailed review and has been approved by the appropriate personnel of the Sponsor (Sarepta Therapeutics, Inc.). The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational drug product.
- 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 and/or new findings, including adverse events, relating to treatment with the investigational drug product.

PPD

PPD

PPD

PPD

PPD

, MD

Date

[redacted]

INVESTIGATOR'S AGREEMENT

I have read Protocol No. 4053-101 (Amendment 8) 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	PPD , MD, PhD	PPD

1. SYNOPSIS

NAME OF COMPANY Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** SRP-4053 Concentrate for solution for infusion **NAME OF ACTIVE INGREDIENT** SRP-4053
TITLE: A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping	
PROTOCOL NUMBER: 4053-101	
PHASE OF STUDY: Phase 1/2	
INVESTIGATOR STUDY SITES: Two-part, multicenter study to be conducted in Europe and in the United States.	

OBJECTIVES:

Part 1: dose titration at 4, 10, 20, and 30 mg/kg/week compared to placebo

Primary objective:

- To evaluate the safety and tolerability of 4 escalating dose levels of SRP-4053 administered once weekly for at least 2 weeks per dose level compared to placebo

Secondary objective:

- To determine the pharmacokinetics (PK) of 4 escalating dose levels of SRP-4053 administered once weekly for at least 2 weeks per dose level compared to placebo

Part 2: weekly open-label SRP-4053 at dose level determined in Part 1 and an untreated group

Primary objectives:

- To assess ambulation, endurance, and muscle function as measured by change from baseline at Week 144 on the 6-Minute Walk Test (6MWT) in treated and untreated patients
- To assess the biological activity of SRP-4053 via dystrophin expression at Week 48 compared to pretreatment

Secondary objectives:

- To assess the safety, tolerability, and PK of SRP-4053 administered weekly
- To assess respiratory function in treated and untreated patients

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- [redacted]
- [redacted]

METHODOLOGY:

This is a first-in-human, multicenter, multiple-dose study to assess the safety, tolerability, efficacy, and PK of once-weekly intravenous (IV) infusions of SRP-4053 in patients with genotypically confirmed Duchenne muscular dystrophy (DMD) with (an) eligible deletion(s) amenable to exon 53 skipping (e.g., 42-52, 45–52, 47–52, 48–52, 49–52, 50–52; 52; 54-58). This study will be conducted in 2 parts.

Part 1 is a randomized, double-blind, placebo-controlled, dose-titration evaluation to assess the safety, tolerability, and PK of 4 dose levels of SRP-4053 in 12 patients with DMD over approximately 12 weeks. Part 2 is a long-term, 168-week, open-label evaluation to assess the efficacy and safety of the selected dose level of SRP-4053 (determined in Part 1) with untreated patients participating in scheduled assessments for 144 weeks. All 12 treated patients from Part 1 will continue in Part 2. Part 2 will also enroll 12 new patients for open-label treatment with

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SRP-4053. These patients must have a clinical diagnosis of DMD confirmed by the finding of a genomic deletion amenable to exon 53 skipping. In addition, up to 24 patients will be enrolled in Part 2 to serve as an untreated group. The patients in the untreated group will be DMD patients with a genotypically confirmed deletion of exon(s) not amenable to treatment by exon 53 skipping, but who otherwise meet the same eligibility criteria as treated patients newly recruited to Part 2.

Part 1

Screening/Baseline Visits

DMD patients will participate in a 4- to 6-week Screening period to ensure eligibility, prior to randomization to SRP-4053 or placebo. Screening assessments include functional testing (6MWT, North Star Ambulatory Assessment [NSAA]), pulmonary function tests (PFTs), an echocardiogram (ECHO), and electrocardiogram (ECG). Blood and urine samples will also be collected for clinical laboratory testing during Screening. Physical examination (including height/weight) will be conducted and vital signs will be assessed at Screening. At Baseline, pretreatment CCI [redacted] will be performed and CCI [redacted] muscle biopsies will be obtained. CCI [redacted] Functional testing at Baseline will include 6MWT, NSAA CCI [redacted] PFTs. CCI [redacted] CCI [redacted]. Serum samples will also be taken at Baseline to provide a pretreatment reference value for immunogenicity. A blood sample will be obtained to determine genotype of selected genes CCI [redacted] CCI [redacted] An ECG will occur and blood and urine samples will be collected for clinical laboratory testing and vital signs will be assessed.

Dose Titration

Twelve patients will be randomized (2:1) to receive SRP-4053 (n = 8) or placebo (n = 4). Patients will receive a weekly IV infusion of placebo or SRP-4053 at escalating dose levels, each for at least 2 weeks: 4 mg/kg/week in Weeks 1-2; 10 mg/kg/week in Weeks 3-4; 20 mg/kg/week in Weeks 5-6; and 30 mg/kg/week beginning on Week 7.

Patients will undergo routine safety evaluations over the course of Part 1. CCI [redacted] CCI [redacted] An ECG will be performed at Week 12; an ECHO will be performed at Week 12. Plasma and urine samples for serial PK determination will be collected at Weeks 1, 3, 5, 7, and 12 in Part 1. Adverse events (AEs) and concomitant medications will be monitored and collected continually over the course of the study.

Dosing in Part 1 will be interrupted or halted if specific predefined stopping criteria are met or if warranted at the discretion of the Sponsor or Investigator. Once the last patient at 30 mg/kg/week has received at least 2 weeks of treatment, an independent Data Safety Monitoring Board (DSMB) will review Part 1 cumulative safety data before dosing in Part 2 can be initiated.

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Part 2

Screening/Baseline Visits

All 12 DMD patients (both SRP-4053 and placebo) from Part 1 will roll over to Part 2 and begin open-label treatment with SRP-4053 at 30 mg/kg/week (or the highest tolerated dose as determined in Part 1) on Week 1 of Part 2. In addition, 12 new treatment-naïve DMD patients with mutations amenable to exon 53 skipping will be enrolled for open-label treatment, along with up to 24 untreated DMD patients with deletion mutations not amenable to exon 53 skipping, who will participate through Week 144. Eligibility of all new Part 2 patients will be confirmed during a 4- to 6-week Screening period (as described in Part 1). New Part 2 patients will also complete Baseline assessments (as described in Part 1). CCI [redacted] a muscle biopsy CCI [redacted] will be obtained from new patients in the treated group at Baseline.

Treatment Phase

Part 2 of the study will not commence until the DSMB has reviewed the cumulative safety data from Part 1. Patients who complete the Part 1 Week 12 visit prior to the completion of the DSMB review will continue to receive blinded weekly infusions of SRP-4053 30 mg/kg or placebo as per their original randomization until after the DSMB review and Part 2 has been approved for initiation.

In Part 2, all patients from Part 1 (including those who previously received placebo) plus an additional 12 new eligible patients will receive SRP-4053 at 30 mg/kg weekly (or the highest tolerated dose determined in Part 1) for up to 168 weeks. All treated patients in Part 2 will be required to undergo a second muscle biopsy at Week 48 of Part 2. Biopsies at Week 48 must occur a) within 2 weeks after the Week 48 visit, b) after the clinical evaluation for Week 48, and c) at least 48 hours after the most recent infusion. After the biopsy procedure, study infusions must not be administered until at least 24 hours post biopsy, and the Investigator must medically clear the patient before the infusion may be given. No further muscle biopsies will be taken after completion of the Week 48 biopsy.

Treated patients will undergo routine safety evaluations over the course of Part 2. Treated patients will also undergo functional testing, PFTs, and an ECG every 12 weeks for the first 48 weeks, then every 24 weeks thereafter; the ECG assessment will be conducted through Week 144. Treated patients in Part 2 will have a CCI [redacted] An ECHO (until Week 144) CCI [redacted] Blood samples for assessment of immunogenicity will be collected every 24 weeks until Week 168. Plasma PK samples from treated patients will be obtained at Weeks 1, 24, 48, 96, and 144. CCI [redacted]

Adverse events and concomitant medications will be monitored and collected continuously over the course of the study.

Untreated patients in Part 2 will not receive SRP-4053, but will undergo the same study assessments as treated patients (except for PK sampling and muscle biopsies), but at a reduced schedule through Week 144.

At Week 144, treated patients must either transition into a long-term extension study or return to the care of their treating physician. If a long-term extension study is not available for enrollment at the patient's Week 144 visit, the patient may transition at Week 168. This study will end after the last SRP-4053-treated patient has either transitioned to a long-term extension study or completed the Part 2 Week 168 study assessments and if applicable, the 4-week safety follow-up visit. Patients who transition to the long-term extension study do not need to complete the 4-week Safety Follow-up Visit.

DURATION OF STUDY:

Screening Period: up to 6 weeks

Part 1: approximately 12 weeks

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Part 2: 168 weeks plus a 4-week safety follow up for a total of 172 weeks.

Total duration for patients participating in both Parts 1 and 2: approximately 190 weeks.

Total duration for untreated patients participating in Part 2: approximately 150 weeks.

NUMBER OF PATIENTS:

Part 1: 12 patients (8 SRP-4053 and 4 placebo)

Part 2: Up to 48 (24 treated patients [12 from Part 1 and 12 new patients] and up to 24 untreated patients)

INCLUSION CRITERIA:

Patients must meet all of the following inclusion criteria to be eligible for this study.

1. Male aged 6 to 15 years, inclusive.
2. For treated patients (all patients in Part 1 and 12 additional treated patients in Part 2), established clinical diagnosis of DMD with a mutation amenable to exon 53 skipping (e.g. deletions of exons such as 42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, or 54-58) as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing.
3. For Part 2 untreated patients, established clinical diagnosis of DMD with a confirmed genomic deletion of exon(s) not amenable to exon 53 skipping as documented by an accredited laboratory and genomic methodology.
4. Have intact right and left biceps muscles or an alternative upper arm muscle group.
5. Have stable cardiac and pulmonary function that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
6. Achieve a mean 6MWT distance of ≥250 meters at both the Screening and Baseline visits (prior to Week 1). The mean 6MWT distance at the Screening and Baseline visits is the average of 2 separate assessments on 2 consecutive days at each visit. The Baseline mean (average of Baseline Day 1 and 2) must be within 15% of the Screening mean (average of Screening Day 1 and 2). (Personal assistance or use of any assistive devices for ambulation is not permitted during the 6MWT.)
7. Patients must meet at least one of the following 2 criteria:
   - NSAA total score >17; or
   - Rise (Gowers') time <7 seconds
8. Have been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: patients are allowed to take other medications (excluding other ribonucleic acid [RNA] antisense or gene therapy agents) including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β-blockers, and potassium provided they have been on a stable dose for at least 12 weeks prior Week 1 and the dose is expected to remain constant throughout the study.
9. Have (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with the study procedure requirements.
10. Be willing to provide informed assent and have (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:

Patients who meet any of the following criteria will be excluded from this study.

1. Use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength or function, within 12 weeks prior to study entry (e.g., growth hormone, anabolic steroids).
2. Previous treatment with the experimental agents BMN-195 (SMT C1100) or PRO053.

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3. Current or previous treatment with any other experimental treatments within 12 weeks prior to study entry. Untreated patients only can be enrolled concurrently in other non-interventional trials, or in interventional trials in which participants are known to be treated with standard-of-care medication, provided they do not interfere with study assessments performed in Study 4053-101, and the patient meets all the protocol-required entry criteria.
4. A left ventricular ejection fraction (LVEF) of <50% (or equivalent fractional shortening) based on the Screening ECHO and QTc (Fridericia's correction) >450 msec.
5. A forced vital capacity (FVC) <50% of predicted value or requirement for nocturnal ventilation.
6. Major surgery within 3 months prior to Week 1 or orthopedic surgery planned for any time during this study which would interfere with the ability to perform outcome measures.
7. Planned use of any aminoglycoside antibiotic or statin within 12 weeks of Week 1 or need for use of an aminoglycoside antibiotic or statin during the study.
8. Presence of other clinically significant illness, for example significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disorder or malignancy.
9. Loss of ≥30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (i.e. fixed loss of >10 degrees plantar flexion from plantigrade assuming normal range of dorsiflexion of 20 degrees).
10. Change in contracture treatment such as serial casting, contracture control devices, night splints, stretching exercises (passive, active, self) within 3 months prior to enrollment, or expected need for such intervention during the study.
11. Prior or ongoing medical condition that, in the Investigator's opinion, could interfere with the patient's participation in the study.

DOSE/ROUTE/REGIMEN:

SRP-4053 concentrate for solution for infusion is supplied as a sterile, clear, colorless, phosphate-buffered saline (PBS) solution in single-use, 2-mL vials with each vial containing 2 mL of SRP-4053 at 50 mg/mL.

REFERENCE TREATMENT:

Part 1: Placebo patients will receive normal saline.

Part 2: None.

CRITERIA FOR EVALUATION:

Part 1

The primary endpoints are:

- Incidence of AEs
- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations
- Incidence of abnormalities on ECGs and ECHOs

The secondary endpoints are the PK parameters of SRP-4053 (see below).

Part 2

Primary Efficacy Endpoint:

Change from baseline at Week 144 in the 6MWT

Primary Biological Endpoint:

Change from baseline at Week 48 in dystrophin protein levels determined by Western blot.

Secondary Efficacy Endpoint:

Change from baseline through Week 144 in FVC percent predicted (FVC%p)

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Secondary Biological Endpoints:

Change from baseline at Week 48 for the following:

- Dystrophin intensity levels determined by immunohistochemistry (IHC)
- Percentage of dystrophin-positive fibers determined by IHC
- Exon 53 skipping determined by measurement and sequence verification of exon 53 skipped messenger RNA

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Safety Endpoints:

- Incidence of AEs
- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations
- Incidence of abnormalities on ECGs and ECHOs
- Immunogenicity

Pharmacokinetic Endpoints:

The PK parameters of SRP-4053 in Part 2 will be determined as described below.

Pharmacokinetics:

Part 1: Full plasma PK sampling (Weeks 1, 3, 5, 7) will be performed at the following time points: immediately predose, at approximately 5 to 10 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of dosing. At Week 12, samples will be collected only at pre-infusion and between 5 and 10 minutes postinfusion. Urine for PK determination will be collected in Part 1 only, on a cumulative basis, during the following time intervals: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, and 12 to 24 hours after the initiation of dosing. PK analysis in Part 1 will be done using noncompartmental methods.

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Part 2: Plasma samples will be obtained from all 24 treated patients in Part 2 pre-infusion and between 5 and 10 minutes postinfusion at Weeks 1, 24, 48, 96, and 144. PK analysis in Part 2 will be done using population PK methods. It may be necessary to combine the data for Parts 1 and 2 to perform population PK analysis adequately.

The following PK parameters will be determined for both Parts 1 and 2, as appropriate:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Area under the plasma concentration-time curve (AUC)
- Apparent volume of distribution at steady state (V_{ss})
- Elimination half-life ($t_{½}$)
- Total clearance (CL)
- Mean residence time (MRT)
- Urinary clearance (CL_R), for Part 1 only

SAMPLE SIZE:

Sample size for this study is based upon qualitative considerations; no formal sample size calculations will be performed.

STATISTICAL METHODS:

Demographic and baseline characteristics will be summarized for Part 1 and Part 2.

Efficacy and Pharmacodynamic Analyses:

All efficacy and biological (ie, pharmacodynamics) endpoints will be summarized descriptively by time point and treatment group for both Part 1 and Part 2. Change from baseline for each of these endpoints will also be summarized by time point and treatment group, if appropriate.

The primary efficacy endpoint of change from baseline at Week 144 (Part 2) in the 6MWT will be summarized by treatment group.

The primary biological endpoint of change from baseline at Week 48 (Part 2) in dystrophin protein level as determined by Western blot will be analyzed based on a 1-sample permutation test.

Other efficacy and biological endpoints will be analyzed similarly to the primary efficacy or biological efficacy endpoint, as appropriate, based on the type of endpoints and the number of assessments during Part 2 of this study.

Safety Analyses:

Safety analyses will be descriptive in nature. Adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. An AE will be considered treatment-emergent if it occurs in the time period starting with the initiation of the first dose of study drug and ending 28 days after the last dose of study drug for treated patients and on or after the Week 1 visit of Part 2 for untreated patients. All AEs will be recorded in the data listings. In general, only treatment-emergent AEs (TEAEs) will be summarized. For all AE tables, the number and percentage of patients reporting AEs will be grouped using the MedDRA SOC and preferred term and summarized treatment group by dose level for the SRP-4053 group. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs. Multiple occurrences of the same AE (at the preferred term level) in the same patient will be counted only once in the frequency tables. If a patient experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to investigational drug product will be used to summarize AEs by relationship and severity.

Descriptive statistics for ECGs, ECHOs, vital signs, physical examinations, and safety laboratory parameters will be generated. All safety data will be presented in the data listings. Additionally, shift and frequency tables of predefined change in abnormal values for select safety parameters will be generated.

Descriptive statistics for the anti-phosphorodiamidate morpholino oligomer (PMO) immune response will be generated. The relationship between anti-PMO antibodies and clinical safety parameters may be assessed. If an

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anti-dystrophin antibody assay or other immunogenicity assays become available during the study, the analysis plan for these endpoints will be detailed in the Statistical Analysis Plan.

Pharmacokinetic Analyses:

The PK of SRP-4053 will be determined from multiple plasma and urine samples collected during Part 1 and from plasma samples collected during Part 2. Individual plasma levels of SRP-4053 will be listed with the corresponding time related to investigational drug product administration and summary statistics will be generated by per-protocol time of collection. Pharmacokinetic parameters for SRP-4053 will be calculated using noncompartmental analysis for Part 1 and using population PK analysis in Part 2. Actual sampling times will be used in all final PK analyses; per-protocol times will be used to calculate mean plasma concentrations for graphical displays. Pharmacokinetic data from Part 2 will be analyzed based on a population PK model using plasma concentration data and appropriate demographic and baseline characteristics.

Interim Analysis:

An interim analysis is planned and will be performed after all treated patients from Part 1 and Part 2 have completed the Week 48 muscle biopsy in Part 2 of the study. The study will be unblinded to the treatment in Part 1 in order to support the interim analysis. In addition, the muscle biopsy samples will be unblinded to treatment status and patient number. The interim analysis will include data for demographic and baseline characteristic, duration of exposure to study drug, and laboratory assessments of muscle biopsy tissue CCI [redacted].

The DSMB will conduct ongoing reviews of the safety data during the study. Administrative reviews of the efficacy results may be conducted (in a blinded fashion for Part 1 data before the interim analysis and in an unblinded fashion for Part 1 data after the interim analysis and Part 2 data) prior to or when all patients complete the Part 2 Week 48 visit, and again when patients complete the Part 2 Week 96 visit.

2. SCHEDULES OF EVENTS

A schedule of study events for Part 1 (double-blind dose titration) is provided in Table 2. The schedules of study events for treated patients are provided in Table 3 (for the first 48 weeks) and Table 4 (for Week 49 through end-of-study [EOS]). In addition, a separate schedule of events for untreated patients in Part 2 is provided in Table 5.

Table 2: Schedule of Events, Part 1: Double-Blind Dose Titration

	SCRN Weeks -6 to -4	BL Weeks -2 to -1	Part 1 (Week)											
			1	2	3	4	5	6	7	8	9	10	11	12[a]
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Document DMD diagnosis	X													
Confirm Eligibility			X											
Randomization[b]			X											
CCI muscle biopsy[c]		X												
CCI														
6MWT[f]	X	X												X
CCI														
Plasma/urine for PK[i]			X		X		X		X					X
Immunogenicity		X	X											X
CCI														
12-lead ECG	X	X												X
ECHO	X													X
Clinical laboratory[j]	X	X	X	X	X	X	X	X	X	X	X			X
Vital signs[k]	X	X	Obtained in association with weekly infusions[k]											
Weight	X		X			X				X				X

Table 2: Schedule of Events, Part 1: Double-Blind Dose Titration

	SCRN Weeks -6 to -4	BL Weeks -2 to -1	Part 1 (Week)											
			1	2	3	4	5	6	7	8	9	10	11	12[a]
Height	X													X
Physical examination	X		X			X				X				X
Dosing[l]			Weekly infusions (dose titration) beginning on Week 1											
DSMB[m]												---------X---------		
Concomitant medications	Continuous													
AE monitoring	Continuous													

[a] Week 12 uses a window of ±1 week. Beginning after the Week 12 visit and until the DSMB decision, scheduled safety assessments for all patients in Part 1 will occur every 4 weeks and functional testing every 12 weeks. Patients whose efficacy assessments (6MWT, CCI [redacted] occurred >4 weeks before the Week 1 visit in Part 2 will repeat all Week 12 assessments prior to starting Part 2.

[b] Randomization (8 SRP-4053 + 4 placebo) will occur at Week 1 prior to first dose.

[c] CCI muscle biopsy procedures performed at the same time prior to first dose once study eligibility is confirmed.

[d] [redacted]

[e] [redacted]

[f] The 6MWT test is to be performed at both Screening and Baseline visits (each on 2 consecutive days) which may require 2-night overnight stays. All other time points will be performed once on 1 day.

[g] [redacted]

[h] [redacted]

[i] Full plasma PK sampling (Weeks 1, 3, 5, 7) will be performed at the following time points: immediately predose, at approximately 5 to 10 minutes after completion of dosing, and approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of dosing. At Week 12, samples will be collected only at pre-infusion and between 5 and 10 minutes postinfusion. Urine for PK sampling will be collected, on a cumulative basis, during the following time intervals: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after initiation of dosing.

[j] Clinical laboratory assessments include: hematology, coagulation, serum chemistry, and urinalysis.

[k] Vital signs include blood pressure, pulse rate, respiration rate, and oral temperature. Patients in the treated and placebo groups will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[l] Randomized patients in Part 1 will be dose-escalated every 2 weeks to receive weekly infusions of SRP-4053 or placebo at: 4 mg/kg/week (Weeks 1-2), 10 mg/kg/week (Weeks 3-4), 20 mg/kg/week (Weeks 5-6), and 30 mg/kg (Week 7-DSMB safety review). The initial 4 patients will be staggered with a minimum of 3 days between administrations of the initial doses to each of these patients. Infusions must be given according to instructions in the Pharmacy Manual. Patients are to be closely monitored for at least 1 hour following the completion of all infusions. Patients in Part 1 who complete Week 12 of Part 1 prior to the completion of the DSMB review will continue to receive weekly dosing.

[m] DSMB safety data evaluation begins once the last patient at 30 mg/kg receives 2 weekly doses.

Table 3: Schedule of Events for Treated Patients in Part 2 (Screening Through First 48 Weeks of Open-Label Treatment)

Note: Part 2 will commence once the DSMB has reviewed safety data from Part 1 to ensure no issues are identified that would preclude Part 2 initiation. Only patients new to Part 2 will undergo Screening to determine Part 2 eligibility and Baseline assessments. Rollover patients from Part 1 will not repeat Screening/Baseline and will begin dosing in Part 2 on Week 1. Patients in Part 1 who complete Week 12 of Part 1 prior to the completion of the DSMB review will continue to receive weekly dosing and undergo safety laboratory testing every 4 weeks and functional testing every 12 weeks. However, Week 12 assessments in Part 1 will have to be (re)done prior to Week 1 in Part 2 (rollover patients only) unless they have been completed within 4 weeks of the Week 1 visit in Part 2. A Schedule of Events for the untreated group is provided in Table 5.

	SCRN[a] Weeks -6 to -4	BL[a] Weeks -2 to -1	Part 2 (Week)																
			1	2-3	4	5-7	8	9-11	12	13-15	16	17-19	20	21-23	24	25-35	36	37-47	48
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Confirm Eligibility[a]			X																
Document DMD diagnosis	X																		
CCI muscle biopsy[b]		X																	X
CCI																			
6MWT[c,f]	X	X							X						X		X		X
PFT (FVC)[c]	X	X							X						X		X		X
CCI																			
Plasma for PK[i]			X												X				X
Immunogenicity		X	X												X				X
CCI																			
12-lead ECG	X	X							X						X		X		X
ECHO[c,j]	X														X				X
Clinical laboratory[k]	X	X	X	X	X		X		X		X		X		X		X		X

Table 3: Schedule of Events for Treated Patients in Part 2 (Screening Through First 48 Weeks of Open-Label Treatment)

Note: Part 2 will commence once the DSMB has reviewed safety data from Part 1 to ensure no issues are identified that would preclude Part 2 initiation. Only patients new to Part 2 will undergo Screening to determine Part 2 eligibility and Baseline assessments. Rollover patients from Part 1 will not repeat Screening/Baseline and will begin dosing in Part 2 on Week 1. Patients in Part 1 who complete Week 12 of Part 1 prior to the completion of the DSMB review will continue to receive weekly dosing and undergo safety laboratory testing every 4 weeks and functional testing every 12 weeks. However, Week 12 assessments in Part 1 will have to be (re)done prior to Week 1 in Part 2 (rollover patients only) unless they have been completed within 4 weeks of the Week 1 visit in Part 2. A Schedule of Events for the untreated group is provided in Table 5.

	SCRN[a] Weeks -6 to -4	BL[a] Weeks -2 to -1	Part 2 (Week)															
			1	2-3	4	5-7	8	9-11	12	13-15	16	17-19	20	21-23	24	25-35	36	37-47	48
Weight[l]	X		X		X		X		X		X		X		X	X[l]	X	X[l]	X
Height	X								X						X		X		X
Vital signs[m]	X	X	Obtained in association with weekly infusions[m]																
Physical examination	X		X		X		X		X		X		X		X		X		X
Dosing[n]			Weekly infusions beginning on Week 1[n]																
Concomitant meds	Continuous																		
AE monitoring	Continuous																		

[a] For new patients entering Part 2.

[b] For patients new to Part 2, CCI muscle biopsy procedures will occur at the same time prior to first dose once study eligibility is confirmed. Then, all patients in Part 2 will be required to undergo a second muscle biopsy at the Week 48 visit. Biopsies at Week 48 must occur a) within 2 weeks after the Week 48 visit, b) after the clinical evaluation for Week 48, and c) at least 48 hours after the most recent infusion. After the biopsy procedure, study infusions must not be administered until at least 24 hours post biopsy, and the Investigator must medically clear the patient before the infusion may be given.

[c] CCI [redacted]

[f] For patients new to Part 2, the 6MWT test is to be performed both at Screening and Baseline visits (each on 2 consecutive days) which may require 2-night overnight stays. All other time points will be performed once on 1 day.

CCI [redacted]

[i] Plasma PK sampling (Weeks 1, 24, 48) will be performed pre-infusion and at approximately 5 to 10 minutes postinfusion.

[j] Rollover patients from Part 1 will have an ECHO every 24 weeks in Part 2. Patients new to Part 2 will have an ECHO at Screening and then every 24 weeks in Part 2.

[k] Clinical laboratory assessments include: hematology, coagulation, serum chemistry, and urinalysis.

[l] Weight measured every 4 weeks.

[m] Vital signs include blood pressure, pulse rate, respiration rate, and oral temperature. Patients in the treated group will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[n] Treated patients in Part 2 (new and rollover patients from Part 1) will receive a weekly infusion of SRP-4053 at 30 mg/kg or highest tolerated dose determined in Part 1. Infusions should be given according to instructions in the Pharmacy Manual. Patients are to be closely monitored for at least 1 hour following the completion of all infusions.

Table 4: Schedule of Events for Treated Patients in Part 2 (Week 49 Through End-of-Study Follow up)

		Part 2 (Week)																			
	49-51	**52**	**53-55**	**56**	**57-59**	**60**	**61-71**	**72**	**73-83**	**84**	**85-95**	**96**	**97-107**	**108**	**109-119**	**120**	**121-131**	**132**	**133-143**	**144**	**156**	**168/ EOS**	**F/U[a]**
CCI																							
6MWT[b,e]								X				X				X				X		X	
PFTs (FVC)[b]								X				X				X				X		X	
CCI																							
Plasma for PK[g]												X								X			
Immunogenicity								X				X				X				X		X	
CCI																							
12-lead ECG								X				X				X				X			
ECHO[b,c]								X				X				X				X			
Clinical laboratory[h]						X		X		X		X		X		X		X		X	X	X	X
Weight[i]						X		X		X		X		X		X		X		X	X	X	
Height								X				X				X				X		X	
Vital signs[j]			Obtained in association with weekly infusions[j] and at 4-week safety follow-up																				
Physical examination						X		X		X		X		X		X		X		X	X	X	X
Dosing[k]		Continuing weekly infusions[k]																					
Concomitant meds			Continuous																				
AE monitoring			Continuous																				

[a] A safety follow-up visit will occur approximately 4 weeks after last dose (approximately Week 172).
[b] Testing uses a window of ±2 weeks.
CCI

[redacted]
c Will be performed once on 1 day.
[redacted]
e Plasma PK sampling (Weeks 96 and 144) will be performed pre-infusion and at approximately 5 to 10 minutes postinfusion.
h Clinical laboratory assessments include: hematology, coagulation, serum chemistry, and urinalysis.
i Weight measured every 12 weeks at the clinic. Infusion must take place at the clinic when weight is to be measured.
j Vital signs include blood pressure, pulse rate, respiration rate, and oral temperature. Patients in the treated group will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.
k Treated patients will receive a weekly infusion of SRP-4053 at 30 mg/kg or highest tolerated dose determined in Part 1. Infusions should be given according to instructions in the Pharmacy Manual. Patients are to be closely monitored for at least 1 hour following the completion of all infusions. At the discretion of the Investigator, optional in-home administration of SRP-4053 by a visiting nurse may be available after Week 48 of Part 2 for visits that do not include functional assessments or safety, PK or CCI [redacted] ECG, ECHO, physical examinations CCI [redacted] For in-home dosing, additional instructions will be provided in a separate manual to the visiting nurse.

Table 5: Schedule of Events for the Untreated Group in Part 2

	SCRN	BL Days -2 to -1	Part 2 (Week)								
			1	12	24	36	48	72	96	120	144/EOS
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Document DMD diagnosis	X										
CCI											
6MWT[a,d]	X	X		X	X	X	X	X	X	X	X
CCI											
12-lead ECG	X	X		X	X	X	X	X	X	X	X
ECHO[a]	X				X		X	X	X	X	X
Clinical laboratory[f]	X	X		X	X	X	X	X	X	X	X
Height and weight	X			X	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X	X
Vital signs[g]	X	X		X	X	X	X	X	X	X	X
Concomitant meds	Continuous										
AE monitoring	Continuous										

Footnotes for Table 5:

[a] Testing uses a window of ±2 weeks.

CCI

[d] The 6MWT test is performed at both Screening and Baseline visits (each on 2 consecutive days), which may require 2-night overnight stays. All other time points will be performed once on 1 day.

[redacted].

Clinical laboratory assessments include: hematology, coagulation, serum chemistry, and urinalysis.

[g] Vital signs include blood pressure, pulse rate, respiration rate, and oral temperature. Patients in the untreated group will have vital signs measured one time per visit.

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations, acronyms, and terms are used in this study protocol.

Abbreviation or term	Definition
2D	2-dimensional
6MWT	6-minute walk test
CCI	
ACE	angiotensin-converting enzyme
CCI	
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	Creatine kinase
CL	total clearance
CL_R	urinary clearance
C_{max}	maximum plasma concentration
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram/echocardiography
EDC	electronic data capture
EOS	End of Study
EP	European Pharmacopeia
FVC	forced vital capacity
FVC%p	forced vital capacity percent predicted
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HEENT	head, eyes, ears, nose, and throat
ICH	International Council for Harmonisation

Abbreviation or term	Definition
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
IVR	interactive voice response
KIM-1	kidney injury molecule 1
LDH	lactase dehydrogenase
CCI	
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
CCI	
MLPA	multiplex ligation-dependent probe amplification
MMWR	Morbidity and Mortality Weekly Report
CCI	
mRNA	messenger ribonucleic acid
CCI	
NOAEL	no observable adverse effect level
NSAA	North Star Ambulatory Assessment
NCS	not clinically significant
PBS	phosphate-buffered saline
CCI	
PFT	pulmonary function test
CCI	
PK	pharmacokinetic(s)
PMO	phosphorodiamidate morpholino oligomer
CCI	
Pre-mRNA	pre-messenger ribonucleic acid
PT	prothrombin time; preferred term
PTT	partial thromboplastin time
CCI	
QOL	quality of life
RNA	ribonucleic acid

Abbreviation or term	Definition
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
Sarepta	Sarepta Therapeutics, Inc.
SOC	system organ class
CCI	[redacted]
SRP-4053	investigational drug product for exon 53 skipping
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
V_{ss}	volume of distribution at steady state
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	white blood cell (count)

5. INTRODUCTION

5.1. Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare (estimated incidence of 1 in 3,500-5000 live births; CDC 2009; Emery 1991), degenerative, X-linked recessive genetic disorder caused by mutations in the dystrophin gene. In DMD, mutations in the dystrophin gene disrupt the open-reading frame, resulting in an absence of functional dystrophin, a critically important part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contraction causes cellular degeneration, regeneration, and inflammation, and over time, myonecrosis. The clinical effect of this disrupted dystrophin reading frame is dramatic and lethal.

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

There are currently no disease-modifying treatments for DMD. Existing interventions are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation. Current pharmacologic treatments, such as corticosteroids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function (Beenakker 2005, Biggar 2006, Pradhan 2006). However, their benefits are only temporary, and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, cushingoid facies and habitus, and cataracts (Biggar 2006, Manzur 2004).

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

Phosphorodiamidate morpholino oligomers (PMOs) are a class of synthetic molecules based on a redesign of the natural nucleic acid structure. PMOs are distinguished from other antisense oligonucleotide platforms due to the use of a 6-member synthetic morpholine ring to bind the nucleobases (as opposed to the 5-member ribose rings in ribonucleic acid (RNA) and deoxyribonucleic acid [DNA]). Moreover, the morpholine rings are linked through CCI [redacted] phosphorodiamidate moieties CCI [redacted]. These differences impart the stability and safety observed with these compounds in nonclinical and clinical studies.

Phosphorodiamidate morpholino oligomers are capable of in vivo binding to pre-messenger ribonucleic acid (pre-mRNA) in a sequence-specific fashion with sufficient avidity to alter the splicing of a pre-mRNA transcript, such as dystrophin. Seventy-nine percent (79%) of boys with DMD have out-of-frame deletions that could be amenable to exon skipping therapies (Aartsma-Rus 2009).

The investigational drug product SRP-4053 is a PMO that selectively binds to exon 53 of dystrophin pre-mRNA. In doing so, it causes the exon to be skipped during processing and restores the mRNA open-reading frame. Approximately 7.7% of all DMD patients (Aartsma-Rus 2009) have deletions amenable to skipping exon 53. In these patients, exon skipping would be expected to enable the production of an internally deleted, yet partially functional, dystrophin protein, similar to that observed in Becker muscular dystrophy (BMD), a much less severe form of dystrophinopathy. In contrast to DMD, most BMD patients remain ambulatory and have a near-normal life expectancy (Bushby 1993).

SRP-4053 is formulated at a drug substance concentration of 50 mg/mL in a sterile, isotonic solution for administration as a weekly intravenous (IV) infusion over 35-60 minutes.

SRP-4053 was evaluated in a series of nonclinical studies including safety pharmacology; absorption, distribution, metabolism, and excretion; and toxicity/toxicokinetics. CCI [redacted]

5.3. Rationale for the Current Study

This is a first-in-human study of SRP-4053 being conducted for the purpose of establishing a clinically effective dose of SRP-4053 in DMD patients amenable to exon 53 skipping, and to assess the safety, pharmacokinetic (PK) and efficacy of SRP-4053 in this population. Part 1 will allow for assessments of safety and PK over increasing dose levels to provide the basis for dose selection for longer term dosing with SRP-4053 in Part 2. CCI [redacted]

6. STUDY OBJECTIVES

6.1. Part 1 (Double-Blind Dose Titration)

6.1.1. Primary Objective

To evaluate the safety and tolerability of 4 escalating dose levels of SRP-4053 administered once weekly for at least 2 weeks per dose level compared to placebo.

6.1.2. Secondary Objective

To determine the PK of 4 escalating dose levels of SRP-4053 administered once weekly for at least 2 weeks per dose level compared to placebo.

6.2. Part 2 (Open-Label and Untreated Patients)

6.2.1. Primary Objectives

- To assess ambulation, endurance, and muscle function as measured by change from baseline at Week 144 on the 6-Minute Walk Test (6MWT) in treated and untreated patients
- To assess the biological activity of SRP-4053 via dystrophin expression at Week 48 compared to pretreatment

6.2.2. Secondary Objectives

- To assess the safety, tolerability, and PK of SRP-4053 administered weekly
- To assess respiratory function in treated and untreated patients

CCI

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a first-in-human, multicenter, multiple-dose study to assess the safety, tolerability, efficacy, and PK of once-weekly IV infusions of SRP-4053 in patients with genotypically confirmed DMD with a deletion amenable to exon 53 skipping (e.g., 42-52, 45-52, 47-52, 48-52, 49-52, 50-52; 52; 54-58). This study will be conducted in 2 parts.

Part 1 is a randomized, double-blind, placebo-controlled, dose-titration evaluation to assess the safety, tolerability, and PK of 4 dose levels of SRP-4053 in 12 patients with DMD over approximately 12 weeks.

Part 2 is a long-term, 168-week, open-label evaluation to assess the efficacy and safety of the selected dose level of SRP-4053 (determined in Part 1) including an untreated group participating in scheduled assessments for 144 weeks. All 12 treated patients from Part 1 will continue in Part 2. Part 2 will also enroll 12 new patients for open-label treatment with SRP-4053. These patients must have a clinical diagnosis of DMD confirmed by the finding of a genomic deletion amenable to exon 53 skipping. In addition, up to 24 patients, who will not receive treatment, will be enrolled in Part 2. The patients in the untreated group will be DMD patients with a confirmed deletion of exon(s) not amenable to treatment by exon 53 skipping, but who otherwise meet the same eligibility criteria as treated patients newly recruited to Part 2. Patients in the untreated group will discontinue the Treatment Phase at Week 144.

Part 1 will be approximately 12 weeks in duration. Part 2 will last up to 168 weeks. Treated patients will have a safety follow-up visit 4 weeks after their last dose on study. Including a 4- to 6-week Screening period, the total study duration (for patients participating in Parts 1 and 2) will be up to 190 weeks. Total duration for untreated patients participating in Part 2 will be up to 150 weeks.

At Week 144, treated patients must either transition into a long-term extension study or return to the care of their treating physician. If a long-term extenstion study is not available for enrollment at the patient's Week 144 visit, the patient may transition at Week 168. This study will end after the last SRP-4053-treated patient has either transitioned to a long-term extension study or completed the Part 2 Week 168 study assessments and if applicable, the 4-week safety follow-up visit. Patients who transition to the long-term extension study do not need to complete the 4-week Safety Follow-up visit.

7.1.1. Part 1 (Double-Blind Dose Titration)

DMD patients will participate in a 4- to 6-week Screening period to ensure eligibility, prior to randomization to SRP-4053 or placebo. Screening assessments include functional testing (6MWT, North Star Ambulatory Assessment [NSAA]), pulmonary function tests (PFTs), an echocardiogram (ECHO), and electrocardiogram (ECG). Blood and urine samples will also be collected for clinical laboratory testing during Screening. Physical examination (including height and weight) will be conducted and vital signs will be assessed as Screening. At Baseline, CCI [redacted] muscle biopsies will be obtained. Muscle biopsies will ensure that pretreatment dystrophin expression is captured for comparison with on-treatment values. CCI [redacted]

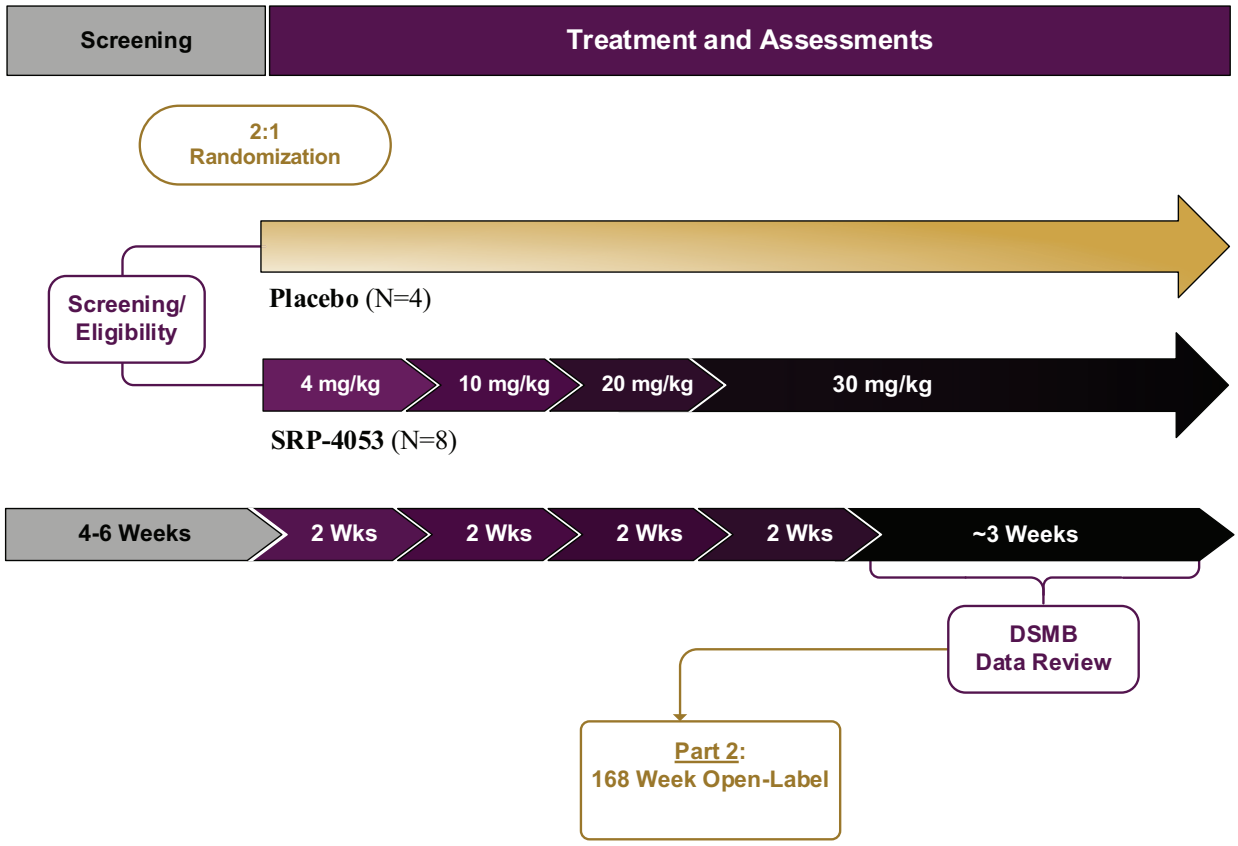
[redacted] Functional testing at Baseline will include 6MWT, [redacted] Serum samples will also be taken at Baseline to provide a pretreatment reference value for immunogenicity. A blood sample will be obtained to determine genotype of selected genes ([redacted]. An ECG will occur and blood and urine samples will be collected for clinical laboratory testing and vital signs will be assessed.

Twelve patients will be randomized (2:1) to receive SRP-4053 (n = 8) or placebo (n = 4). Patients will receive a weekly IV infusion of placebo or SRP-4053 at escalating dose levels, each for at least 2 weeks: 4 mg/kg/week in Weeks 1-2; 10 mg/kg/week in Weeks 3-4; 20 mg/kg/week in Weeks 5-6; and 30 mg/kg/week beginning at Week 7. Refer to Section 9.7 for specific details regarding spacing of initial doses between patients and dose titration in Part 1.

Patients will undergo routine safety evaluations over the course of Part 1. [redacted] An ECG will be performed at Weeks 7 and 12; an ECHO will be performed at Week 12. Plasma and urine samples for serial PK determination will be collected on Weeks 1, 3, 5, 7, and 12 in Part 1. Adverse events (AEs) and concomitant medications will be monitored and collected continuously over the course of the study.

Figure 1 is a schematic of the study design for Part 1.

Figure 1: Study Schematic for Part 1, Double-Blind Dose Titration



Blinded safety data from Part 1 will be reviewed by an independent Data Safety Monitoring Board (DSMB) prior to the initiation of dosing in Part 2. Once the last patient at 30 mg/kg/week has received at least 2 weeks of treatment, the DSMB will review the cumulative safety of Part 1 before dosing in Part 2 can commence. The dose chosen for Part 2 may be lower than 30 mg/kg/week based on the safety review of Part 1 of the study.

Patients who complete the Part 1 Week 12 visit prior to the completion of the DSMB review will continue to receive blinded weekly infusions as per their original randomization until the DSMB review is complete and Part 2 has been approved for initiation. During this unscheduled treatment period of continued dosing after Part 1 Week 12, patients will undergo safety laboratory assessments every 4 weeks and functional assessments every 12 weeks (Table 6).

Table 6: Study Procedures after Part 1 Week 12 up to Start of Part 2

Visit Type	Part 1 Study Week[a]	Study Procedures/Assessments Performed
Standard Dosing Visit (weekly)	13, 14, 15, 16, 17, 18, 19, 20…	IV Infusion of SRP-4053 or Placebo; Vital Signs; Adverse Events; Concomitant Medications
Dosing and Safety Assessment Visit (every 4 weeks)	16, 20…	All procedures/assessments of Standard Dosing Visit, plus: Safety Laboratory Collection (blood, urine); Weight; Height; Physical Examination
Dosing, Safety and Functional Assessment Visit (every 12 weeks, and prior to start of Part 2 if >4 weeks since last functional assessment)	24… And within 4 weeks prior to first dosing visit in Part 2	All procedures/assessments of Dosing and Safety Assessment Visit, plus: 6MWT, CCI [redacted] ECHO, ECG

[a] The number of weeks each patient participates in Part 1 will vary depending on when the patient entered the study and when his Part 2 begins.

7.1.2. Part 2 (Open-Label and Untreated Patients)

Dosing in Part 2 of the study will not commence until the DSMB has reviewed cumulative safety data from Part 1 to ensure no safety issues are identified.

Screening/Baseline Visits

All 12 DMD patients (both SRP-4053 and placebo) from Part 1 will roll over to Part 2 and begin open-label treatment with SRP-4053 at 30 mg/kg/week (or the highest tolerated dose determined in Part 1) on Week 1 of Part 2. In addition, 12 new treatment-naïve DMD patients with mutations amenable to exon 53 skipping will be enrolled for open-label treatment, along with up to 24 DMD patients with deletion mutations not amenable to exon 53 skipping who will not receive treatment with SRP-4053. Eligibility of all new Part 2 patients will be confirmed during a 4- to 6-week Screening period (as described in Section 7.1.1). New Part 2 patients will also complete Baseline assessments (as described in Section 7.1.1). CCI [redacted] for all new Part 2 patients and a muscle biopsy CCI [redacted] will be obtained from new patients in the treated group at Baseline.

Treatment Phase

In Part 2, all patients from Part 1 (including those who previously received placebo) plus an additional 12 new eligible patients will receive SRP-4053 at 30 mg/kg weekly (or the highest tolerated dose determined in Part 1) for up to 168 weeks. Untreated patients will discontinue the Treatment Phase at Week 144. All treated patients in Part 2 will be required to undergo a second muscle biopsy at Week 48 of Part 2. Biopsies at Week 48 must occur a) within 2 weeks after the Week 48 visit; b) after the clinical evaluation for Week 48, and c) at least 48 hours after the most recent infusion. After the biopsy procedure, study infusions must not be administered until at least 24 hours post biopsy, and the Investigator must medically clear the patient before the

infusion may be given. No further muscle biopsies will be taken after completion of the Week 48 biopsy.

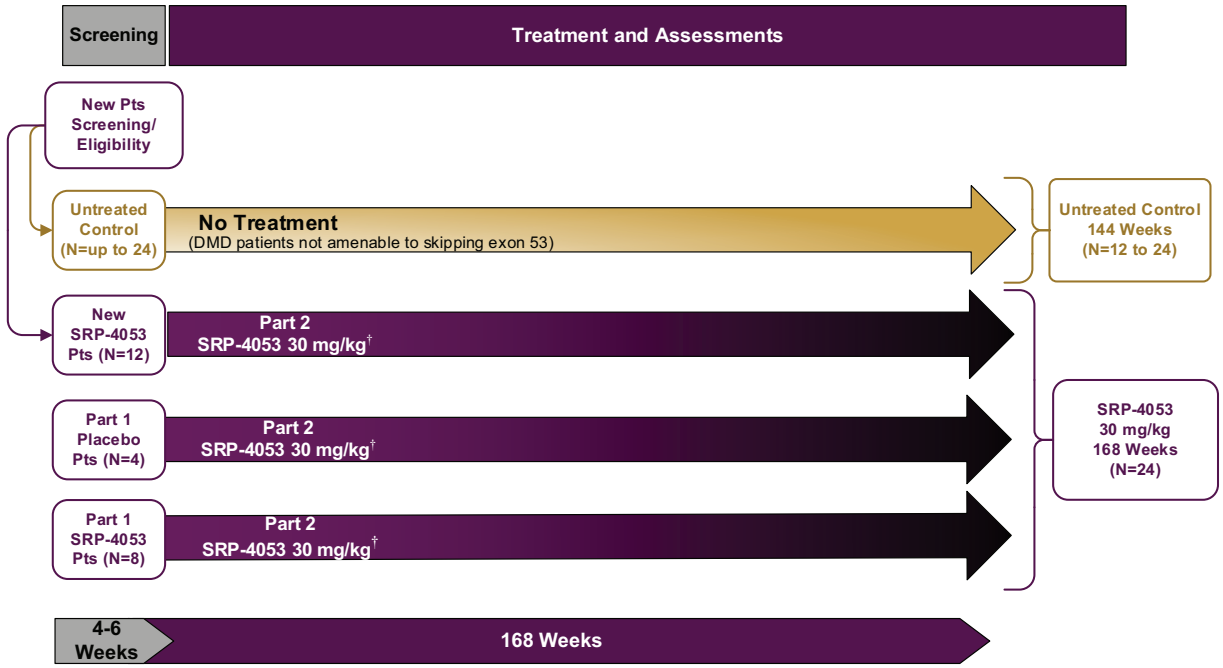
Treated patients will undergo routine safety evaluations over the course of Part 2. Treated patients will also undergo functional testing, PFTs, and an ECG every 12 weeks for the first 48 weeks, then every 24 weeks thereafter; the ECG assessment will be collected through Week 144. Treated patients in Part 2 will have CCI [redacted] An ECHO (until Week 144) CCI [redacted] CCI [redacted] Blood samples for assessment of immunogenicity will be collected every 24 weeks until Week 168. Plasma PK samples from treated patients will be obtained at Weeks 1, 24, 48, 96, and 144. CCI [redacted] Adverse events and concomitant medications will be monitored and collected continuously over the course of the study.

Untreated patients in Part 2 will not receive SRP-4053, but will undergo the same study assessments as treated patients (except for PK sampling and muscle biopsies), but at a reduced schedule until Week 144 (Table 5). Untreated patients will continue to receive their current standard of care for their disease.

For treated patients only and only for visits that do not include functional assessments or safety, PK or CCI [redacted] ECG, ECHO, physical examinations, CCI [redacted], optional in-home administration of SRP-4053 by a visiting nurse may be available, with Investigator approval, after patients have completed Week 48 of Part 2.

Figure 2 is a schematic of the study design for Part 2.

Figure 2 Study Schematic for Part 2, Open-Label and Untreated Patients



† Or maximum tolerated dose as determined in Part 1

7.2. Study Endpoints

The following study endpoints will be evaluated in this study. Descriptions of all study assessments and procedures are provided in Section 10.

7.2.1. Part 1

The primary endpoint in Part 1 is the safety of SRP-4053, assessed as follows:

- Incidence of AEs
- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations
- Incidence of abnormalities on ECGs and ECHOs

The secondary endpoint in Part 1 is to determine the following pharmacokinetic parameters:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Area under the plasma concentration-curve (AUC)
- Apparent volume of distribution at steady state (V_{ss})
- Elimination half-life ($t_{½}$)
- Total clearance (CL)

- Mean residence time (MRT)
- Urinary clearance (CL_R)

7.2.2. Part 2

7.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline at Week 144 in the 6MWT.

7.2.2.2. Primary Biological Endpoint

The primary biological endpoint is the change from baseline at Week 48 in dystrophin protein levels determined by Western blot.

7.2.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoint is the change from baseline through Week 144 in forced vital capacity percent predicted (FVC%p)

7.2.2.4. Secondary Biological Endpoints

Secondary biological endpoints include the change from baseline at Week 48 for the following:

- Dystrophin intensity levels determined by immunohistochemistry (IHC)
- Percentage of dystrophin-positive fibers as determined by IHC
- Exon 53 skipping determined by measurement and sequence verification of exon 53 skipped mRNA

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[redacted]

7.2.3. Safety Endpoints

- Incidence of AEs
- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations
- Incidence of abnormalities on ECGs and ECHOs
- Immunogenicity

7.2.4. Pharmacokinetic Endpoints

- C_{max}
- t_{max}
- AUC
- V_{ss}
- $t_{½}$
- CL
- MRT
- CL_R, Part 1 only

7.3. Discussion of Study Design

7.3.1. Choice of Study Population

Duchenne muscular dystrophy is a rare disease that occurs in approximately 1 in 3500-5000 males worldwide. Approximately 7.7% of patients have mutations in the dystrophin gene that are amenable to skipping exon 53 (Aartsma-Rus 2009). Only ambulatory patients at least 6 of age are eligible to participate in this study as patients must be able to complete the primary efficacy assessment (the 6MWT, Section 10.2.1) and be at an age where, based on natural history data, a decline rather than increase in the 6MWT is expected over the duration of the study. Because DMD is a rare disease, the accrual of patients for enrollment may be

challenging. To allow for efficient recruitment of the appropriate patient population, this study is being conducted at multiple sites. The selected sites for this study are centers of excellence for treatment of DMD, have extensive experience collaborating on clinical trials, and are therefore optimally suited to enroll and conduct the present study.

Part 1 is a randomized and placebo-controlled dose titration where patients will be randomized (2:1, SRP-4053:placebo) to receive once-weekly infusions at each dose level for at least 2 weeks beginning at 4 mg/kg/week and followed by 10 mg/kg/week, 20 mg/kg/week, and 30 mg/kg/week. A double-blind, placebo-control design will be used to reduce potential bias during data collection and evaluation of clinical (safety) parameters.

Part 2 will evaluate the proposed therapeutic dose (target of 30 mg/kg or the highest tolerated dose determined in Part 1) as a once-weekly open-label infusion for up to 168 weeks.

Part 2 of this study will also enroll up to 24 patients with DMD with a confirmed deletion of exon(s) that are not amenable to exon 53 skipping that will not receive treatment with SRP-4053. This patient group will also have deletions in the spectrin-like repeating units and have a similar phenotype with regard to disease manifestations and rate of progression.

7.3.2. Duration of Study

In Part 1, a treatment duration of approximately 12 weeks (at least 2 weeks per dose level x 4 dose levels in addition to a 3- to 4-week DSMB safety review) is considered appropriate for dose escalation (dose titration) of SRP-4053 to obtain sufficient safety data to determine whether dosing in Part 2 can be initiated.

In Part 2, a treatment duration of up to 168 weeks was chosen for open-label dosing based on clinical studies of eteplirsen, a PMO designed to skip exon 51 of the dystrophin gene. Based on clinical experience with eteplirsen, dystrophin-positive fibers may be detectable by the 24th week of treatment; however, changes in functional clinical endpoints measuring endurance and muscle function may not be evident until at least 96 weeks of treatment. The 168-week treatment period and 4-week safety follow-up will also allow for long-term assessment of safety.

7.3.3. Choice of Efficacy Endpoints

The 6MWT was selected as the primary efficacy endpoint as it is the most reliable and sensitive instrument currently available to demonstrate a functional change in ambulation and endurance for DMD patients. The 6MWT is a frequently used measure of functional capacity with regard to both strength and endurance and is one that has been used as a primary outcome measure in clinical trials in ambulatory DMD patients to assess other potentially disease-modifying drugs such as ataluren and drisapersen. Based on data from natural history and placebo-controlled interventional studies, patients with DMD who have the walking distance and age range of the population as defined in the inclusion criteria (Section 8.1) are expected to lose up to 100 meters over the course of 1 year (McDonald 2010, Bushby 1993, Mazzone 2011).

The percentage of dystrophin-positive fibers relative to normal (100%) was selected as the primary biological efficacy endpoint as the very low percentage of such fibers observed in DMD patients is a hallmark of the disease. The intended effect of exon skipping treatments such as SRP-4053 is to increase levels of dystrophin protein expression.

Other secondary efficacy endpoints were chosen based on their relevance to the evaluation of a progressive disease such as DMD. CCI [redacted]

8. PATIENT POPULATION AND SELECTION

8.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for this study.

1. Male aged 6 to 15, inclusive.
2. For treated patients (all patients in Part 1 + 12 additional treated patients in Part 2), established clinical diagnosis of DMD amenable to exon 53 skipping (e.g., deletions of exons such as 42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, or 54-58) as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing.
3. For Part 2 untreated patients, established clinical diagnosis of DMD with a confirmed genomic deletion of exon(s) not amenable to exon 53 skipping as documented by an accredited laboratory and genomic methodology.
4. Have intact right and left biceps muscles or an alternative upper arm muscle group.
5. Have stable cardiac and pulmonary function that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
6. Achieve a mean 6MWT distance of ≥250 meters at both the Screening and Baseline visits (prior to Week 1). The mean 6MWT distance at the Screening and Baseline visits is the average of 2 separate assessments on 2 consecutive days at each visit. The Baseline mean (average of Baseline Day 1 and 2) must be within 15% of the Screening mean (average of Screening Day 1 and 2). (Personal assistance or use of any assistive devices for ambulation is not permitted during the 6MWT.)
7. Patients must meet one of the following 2 criteria:
   - NSAA total score >17; or
   - Rise (Gowers') time <7 seconds
8. Have been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: patients are allowed to take other medication (excluding other RNA antisense or gene therapy agents) including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β-blockers, and potassium provided they have been on a stable dose for at least 12 weeks prior Week 1 and the dose is expected to remain constant throughout the study.
9. Have (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with the study procedure requirements.
10. Be willing to provide informed assent and have a parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the patient to participate in the study.

8.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this study.

1. Use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength or function, within 12 weeks prior to study entry (e.g., growth hormone, anabolic steroids).
2. Previous treatment with the experimental agents BMN-195 (SMT C1100) or PRO053.
3. Current or previous treatment with any other experimental treatments within 12 weeks prior to study entry. Untreated patients only can be enrolled concurrently in other non-interventional trials, or in interventional trials in which participants are known to be treated with standard-of-care medication, provided they do not interfere with study assessments performed in Study 4053-101, and the patient meets all the protocol-required entry criteria.
4. Have a left ventricular ejection fraction (LVEF) of <50% (or equivalent fractional shortening) based on the Screening ECHO and QTc (Fridericia's correction) >450 msec.
5. Have a forced vital capacity (FVC) <50% of predicted value or require nocturnal ventilation.
6. Major surgery within 3 months prior to Week 1 or planned orthopedic surgery for any time during this study, which would interfere with the ability to perform outcome measures.
7. Use of any aminoglycoside antibiotic or statin within 12 weeks of Week 1 or need for use of an aminoglycoside antibiotic or statin during the study.
8. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease or malignancy.
9. Loss of ≥30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (i.e., fixed loss of >10 degrees plantar flexion from plantigrade assuming normal range of dorsiflexion of 20 degrees).
10. Change in contracture treatment such as serial casting, contracture control devices, night splints, stretching exercises (passive, active, self) within 3 months prior to enrollment, or expected need for such intervention during the study.
11. Prior or ongoing medical condition that, in the Investigator's opinion, could interfere with the patient's participation in the study.

8.3. Completion of a Patient's Participation and Overall Study Completion

The length of a patient's participation in Part 1 will be from the time the informed consent form is signed until completion of the Week 12 assessments or until the DSMB has met and evaluated Part 1 safety data prior to the beginning of Part 2, whichever is later. Patients who receive open-label treatment in Part 2 will have completed the study when they transition to a long-term extension study or complete the Week 168 study assessments in Part 2 plus the 4-week safety

follow-up visit. Untreated patients in Part 2 will have completed the study when they complete the Week 144 assessments (the 4-week safety follow-up visit is not applicable).

8.4. Patient Withdrawal Criteria

Any patient in either Part 1 or Part 2 can decide to withdraw from study participation at any time for any reason. In addition, the study Sponsor may decide to stop the study participation of any patient as deemed necessary. The Principal 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 (i.e., was found to not have met the eligibility criteria).
- The patient experiences an intolerable or unacceptable AE.
- The patient is unable to comply with the requirements of the protocol.

The Investigator or study staff will document the reason(s) for treatment discontinuation in source documents. Patients who receive at least one (1) dose of investigational drug product who are withdrawn from treatment will be asked to complete all early termination assessments within 30 days of withdrawal. For Part 1, these assessments will include those listed for Week 12 (Table 2); for Part 2 these assessments will include those listed for Week 168 (Table 4). Patients in the untreated group who complete Baseline assessments and who are withdrawn from the study will be asked to complete all early termination assessments within 30 days of withdrawal (see Week 144 assessments on Table 5). Patients who withdraw from the study will not be replaced.

9. TREATMENTS

9.1. Investigational Drug Product

Details regarding the investigational drug product in this study, SRP-4053 concentrate for solution for infusion, are described in the following sections. For dosing considerations, please refer to Section 9.7.

9.2. Packaging and Labeling

In Part 1, SRP-4053 concentrate for solution for infusion is supplied as a sterile, clear, colorless, phosphate-buffered saline (PBS) solution in single-use, 2-mL vials with each vial containing 2 mL of SRP-4053 at a concentration of 50 mg/mL.

The label text for the investigational product will comply with applicable regional, national, and local laws and regulations and will include at a minimum the contents of the vial, the appropriate cautionary statements, lot number, storage conditions, and the name of the Sponsor (Sarepta Therapeutics, Inc.). The protocol number will also be included on EU supplies only.

Placebo patients in Part 1 will receive 0.9% normal saline, United States Pharmacopeia/European Pharmacopeia (USP/EP).

For Part 2, SRP-4053 concentrate for solution for infusion will be packaged and labeled as described above for SRP-4053 in Part 1.

9.3. Receipt of Investigational Drug Product

A proof of receipt, which details the quantity and description of the investigational product, will accompany the shipment from the Sponsor or designee to the Investigator. Details for investigational product receipt, storage, and dispensation recordkeeping are located in the study-specific Pharmacy Manual. The Investigator must ensure that the investigational product is maintained in a controlled location, with limited access and temperature monitoring, and under appropriate storage conditions.

9.4. Storage

Vials of investigational drug product must be stored according to manufacturer specifications at a consistent temperature from 2°C to 8°C in a secured, limited-access area with temperature recording, controls and monitoring. Details for preparation of the investigational drug product for administration can be found in the study-specific Pharmacy Manual.

9.5. Disposition of Unused Investigational Drug Product

All unused investigational drug product vials must be maintained under adequate storage conditions in a limited-access area until time of use. Upon completion of the study, any remaining unused investigational drug product vials will be returned to the Sponsor or be destroyed per the site-specific standard operating procedures. Final drug accountability will be monitored by the Sponsor or their representative.

9.6. Administration of Investigational Drug Product

Refer to the Pharmacy Manual for specific information regarding the administration of investigational drug product.

9.6.1. Part 1 (Double-Blind Dose Titration)

In Part 1, 12 patients will be randomized (2:1) to receive SRP-4053 (n = 8) or placebo (n = 4) (Section 9.7). Patients will receive a weekly IV infusion of placebo, or SRP-4053 at dose levels escalating every 2 weeks: 4 mg/kg/week in Weeks 1-2; 10 mg/kg/week in Weeks 3-4; 20 mg/kg/week in Weeks 5-6; and 30 mg/kg/week beginning on Week 7.

Blinded qualified study staff will administer SRP-4053 drug product as an IV infusion according to instructions in the Pharmacy Manual. The dose of SRP-4053 or placebo will be calculated based on the most recent patient weight obtained according to the schedule of events for Part 1 (Table 2). All patients will be closely monitored for at least 1 hour following the completion of each infusion.

Refer to Section 9.7 for dosing considerations including dose interruption, safety review, and stopping rules.

9.6.2. Part 2

Before dosing can be initiated in Part 2, an independent DSMB will review safety data from the Part 1 dose titration. Any patients who complete Part 1 Week 12 visit prior to the completion of the DSMB review will continue to receive blinded weekly infusions of SRP-4053 30 mg/kg or placebo as per their original randomization until after the DSMB review and Part 2 has been approved for initiation. If no safety issues are identified to preclude the initiation of dosing in Part 2, Part 2 will commence.

In Part 2, all treated patients (12 from Part 1 plus 12 new patients amenable to exon 53 skipping) will receive 30 mg/kg of SRP-4053 (or the highest tolerated dose determined in Part 1) administered as an IV infusion according to the steps detailed in the study-specific Pharmacy Manual. The dose of SRP-4053 will be calculated based on the most recent patient weight obtained according to the schedule of events (Table 3 and Table 4). All patients will be closely monitored for at least 1 hour following the completion of all infusions. For visits that do not include functional assessments or safety, PK or CCI [redacted] ECG, ECHO, physical examinations, CCI [redacted], optional in-home administration of SRP-4053 by a visiting nurse may be available after Week 48 of Part 2, at the discretion of the Investigator. For in-home dosing, additional instructions will be provided in a separate manual to the visiting nurse.

Part 2 untreated patients (up to 24 DMD patients with exon deletions not amenable to exon 53 skipping) will continue to receive their current standard of care and will not receive any investigational product.

9.7. Dosing Considerations

9.7.1. General Considerations

As a class of compounds, PMOs show low protein binding and consistent pharmacology. PMOs have low potential for drug-drug interactions since PMOs are not metabolized and do not interact with cytochrome P450 or drug transporters at biologically relevant concentrations. The predominant biologic effects of PMOs arise from selective hybridization with their intended RNA targets.

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9.7.3. Rationale for Dose Increase

Patients enrolled and randomized into Part 1 of the study to receive SRP-4053 will receive 2 weekly infusions each at 4, 10, and 20 mg/kg of SRP-4053 and will then transition to 30 mg/kg/week for the remainder of the study.

The low 2- to 2.5X dose increase to subsequent dose levels decreases the risk of new high-level toxicity not already apparent in milder form at the previous doses. Furthermore, the gradual dose titration within each individual patient will further increase the likelihood of early detection of any potential dose-dependent safety signals and thus allow for earlier intervention than would be possible with a sequential dose-escalation cohort design. All patients will be carefully monitored during dosing in Part 1 (Section 9.8.2). In addition, strict stopping rules will be followed during dose escalation (Section 9.8.3).

Dose initiation for the first 4 patients will be staggered, with a minimum of 3 days between administrations of the initial doses to these patients (Table 2). Dosing of additional patients can therefore be precluded in the event of occurrence of unexpected acute or subacute safety issues.

Increases of dose levels every 2 weeks is considered appropriate given the short plasma half-life of SRP-4053 compared to the dosing interval, and the absence of accumulation.

9.7.4. Dose Modification, Reduction, or Delay

There is no provision for dose alteration in this study. If a patient experiences an AE that requires interruption of administration of investigational drug product for >2 weeks, the Investigator will consult with the Medical Monitor to determine whether the patient may resume treatment or whether he needs to be excluded from further dosing. Refer to Section 9.8.2 for safety monitoring procedures for dose escalation in Part 1.

9.8. Safety Considerations

9.8.1. General Safety Precautions

This study is being conducted at clinical trial centers equipped with state-of-the-art medical equipment. Trained medical personnel will be present during the entire dosing period and for at least 1 hour after each dose to monitor each patient. Resuscitation equipment will be readily available for immediate use during dose administration and follow up, and patients will not be allowed to leave the clinic until the Investigator or designated physician has ascertained that they can do so safely.

Safety assessments will include routine clinical and laboratory evaluations. Refer to Section 9.8.2 and to the schedules of events for treated patients (Table 2, Table 3, and Table 4) and untreated patients (Table 5). In addition, ECGs and ECHOs will be performed as outlined in the schedules of events.

The most likely potential AEs based on the nonclinical safety profile of SRP-4053 are expected to be related to renal function. As such, safety monitoring in this study includes testing to detect events representative of renal toxicity (such as proteinuria). CCI

As a precautionary measure based on clinical experience with oligonucleotide therapeutics with a different backbone structure (i.e., phosphorothioate oligomers), potential occurrence of infusion reactions as well as coagulation parameters will also be monitored.

The Investigator at the surgical site and the surgeon performing the muscle biopsies (for treated patients only) are responsible for ensuring that the anesthesiologist is familiar with the anesthesia guidelines for DMD patients, which are designed to enhance patient safety.

9.8.2. Safety Monitoring During Dose Titration

The following procedures will be implemented to minimize the risk to study patients during dose titration in Part 1.

- All serious adverse events (SAEs), regardless of relatedness, will be reported by the Investigators to the Sponsor immediately and within 24 hours of awareness.
- All AEs classified as possibly/probably or definitely related to investigational drug product, regardless of severity, will be reported by the Investigators to the Sponsor immediately, within 48 hours of awareness.

- The Medical Monitor will review safety data including clinical and laboratory information on an ongoing basis. Summary reports of these reviews will be distributed as warranted to all participating Investigators, specifically when treatment-related AEs have been reported.
- Prior to dose administration, the Investigator will review all AEs and all laboratory values for the specific patient and will only proceed with dosing if he or she deems that it is safe to do so based on all available information.

9.8.3. Stopping Rules

Safety data review including AEs and laboratory assessments will be performed on an ongoing basis. During the dose escalation in Part 1, sites are required to report all AEs as defined in Section 9.8.2 and Section 11. If safety concerns arise at any time, dosing may be stopped until these concerns have been addressed. Dosing in Part 1 will be interrupted to allow for review of cumulative safety data by the DSMB if any of the following conditions are met:

- ≥2 severe AEs or ≥3 moderate AEs considered to be possibly/probably or definitely related to investigational drug product
- Any SAE considered to be possibly/probably or definitely related to investigational drug product
- ≥2 patients develop 2 consecutive serum creatinine levels ≥2X their respective average pretreatment values
- ≥2 patients develop a confirmed unexplained proteinuria of >2+
- Any unexplained gamma-glutamyl transferase (GGT) >3X upper limit of normal (ULN) in combination with bilirubin >2X ULN
- Any unexplained partial thromboplastin time (PTT) >45 seconds

The DSMB will be notified by the Sponsor within 24 hours of the Sponsor learning of any of the events listed above. Dosing may also be interrupted or halted if warranted at the discretion of the Sponsor or Investigator. Should this occur, re-initiation of dosing may be permitted via protocol amendment if deemed appropriate following safety data review by the Sponsor and the DSMB. Any decisions related to dose adjustment, delay, or stopping during dose titration will be communicated by the Sponsor to all sites immediately. In addition, Investigators may, in the event of an emergency, directly contact their peers at other sites to communicate safety concerns.

9.8.4. Data Safety Monitoring Board

An independent DSMB will be commissioned to assist in the evaluation of safety data during the blinded dose escalation in Part 1 and to review aggregate safety data before Part 2 dosing is initiated. This formal DSMB review will be based on all available safety data for all patients at the time point when the last patient in Part 1 has completed Week 8 dosing (received 2 doses of the highest dose of investigational drug product). This data review will be blinded unless the DSMB specifically requests unblinding based on safety data summaries. The DSMB will be charged with determining whether transitioning into Part 2 of the protocol is appropriate based on aggregate safety data from Part 1. After initiation of Part 2, periodic reviews of safety data

will be conducted by the DSMB as outlined in the DSMB charter, and the Part 1 blind will be maintained unless knowledge of the treatment assignments is necessary for the evaluation of safety.

Any decision to interrupt, restart, or discontinue the study will be made by the Sponsor in consultation with the DSMB.

A formal DSMB meeting may be convened at any time if requested by one or more Investigators and/or the Sponsor of this study. The DSMB charter provides further detail on the meeting and decision-making process involving the DSMB.

The outcome of any DSMB meeting will be communicated to the Investigators by the Sponsor or responsible designee. The relevant regulatory authorities will be promptly notified of study suspension or discontinuation related to safety concerns. Any suspension or discontinuation of the trial for any reason will also be promptly reported to the relevant Institutional Review Board/Independent Ethics Committee (IRB/IEC).

9.9. Randomization and Blinding

9.9.1. Randomization

After qualifying for study entry in Part 1, DMD patients with an out-of-frame deletion confirmed as amenable to exon 53 skipping will be randomized using a 2:1 ratio to either SRP-4053 (8 patients) or placebo (4 patients). Randomization will be performed prior to dosing on Week 1 using an interactive voice response (IVR) system.

9.9.2. Blinding for Dose Administration

Part 1 is a double-blind, placebo-controlled dose titration where all patients, parents, Investigators, and all site staff not involved with study drug preparation will be blinded to treatment assignment. A double-blind, placebo-controlled design will be used to reduce potential bias during data collection and evaluation of outcome parameters.

Eight patients will receive weekly escalating IV doses of SRP-4053 and 4 patients will receive weekly escalating IV doses of placebo in a blinded fashion over 12 weeks. Other individuals (qualified back-up pharmacists) who are authorized to verify dose and dose assignment will be unblinded to treatment assignment. These individuals will not have interaction with study participants and will be instructed not to divulge randomization assignment to others under any circumstances unless directed to do so by the Investigator in the interest of patient safety.

In Part 2, all treated patients (rollover patients from Part 1 and patients new to Part 2 who are amenable to exon 53 skipping) will receive open-label SRP-4053 (at the dose determined in Part 1) as a weekly IV infusion for 144 weeks. No blinding is required.

9.9.3. Blinding for Clinical Evaluators

To minimize assessment bias, clinical evaluators will be trained on how to maintain blinding to treatment as best as possible. Specifically, clinical evaluators will:

- Not be involved in any aspect of care for the patients over the course of the study and will not have access to any clinical patient records including laboratory values, genetic analyses, or study-specific assessment and treatment schedules.
- Avoid conversation with parents, caregivers and the patients about treatment, other assessments including muscle biopsies, and any other disease-related topics.

In order to maintain the study blind, interaction between parents and clinical evaluators will be minimized. Parents, caregivers and patients will be instructed not to discuss their study participation with the clinical evaluators. Parents/caregivers of study participants will be informed that information on their child's performance on assessment measures (unless of clinical significance and requiring intervention) will be not be shared during the course of the study. Parents/caregivers will also be discouraged from attempting to access information on performance of other study participants and will be instructed not to publicly discuss their child's participation in this trial.

9.9.4. Blinding for Laboratory Assessments

Biological laboratory assessments, notably IHC and Western blotting, will be done in a blinded fashion so that the raters are unaware of the time point and treatment group under which the sample has been taken. Images will have all capture date information removed and will be secured in a location that is not accessible to the analyst or pathologist(s) who will perform the blinded automated algorithm analysis of dystrophin-positive fibers and assessment of dystrophin-associated protein localization at the sarcolemma membrane.

The total amount of dystrophin protein will be assessed using semi-quantitative IHC in a central laboratory utilizing predefined standardized methodology and evaluated by a blinded pathology expert.

Processed muscle biopsy tissue from patients will be analyzed using Western blot to quantitate the amount of dystrophin protein. Western blot analysis will be performed by blinded personnel at the end of the study that will be blinded to the treatment group and time point of the patient's muscle biopsy.

The laboratory analysis of muscle biopsy tissue, IHC, and quantification of dystrophin (by Western blot) will be performed after all patients have completed the Week 48 muscle biopsy. Once the analysis is complete, the results will be unblinded to treatment status and patient study number.

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

9.9.5. Unblinding Procedures

In the event of a medical emergency wherein the knowledge of the patient's treatment assignment may influence clinical decision-making, the Investigator has the option to unblind treatment assignment (applicable to Part 1 only) using the IVR system. Please see Section 11.6.3 for additional information regarding unblinding in emergency situations.

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

If deemed necessary, the DSMB may request to review unblinded safety data at any time to ensure the safety of any individual patient or the study population as a whole. Data access will be restricted to DSMB members.

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

9.10. Prior and Concomitant Medications and Therapeutic Procedures

The following therapies may be used prior to enrollment and throughout the study at the discretion of the Investigator. However, attempts should be made to keep the dosage constant throughout the treatment period.

- Oral corticosteroids for treatment of DMD including, but not limited to prednisolone, prednisone, and deflazacort. Patients entering the study must have been on a stable dose (or dose equivalent) of oral corticosteroids for at least 24 weeks prior to the first administration of study treatment at Week 1. Doses of corticosteroids are expected to remain constant (except for modifications to accommodate changes in weight) through the completion of study to the degree that is clinically feasible. Prior to and during the study, it is acceptable to change the specific oral corticosteroid as clinically necessary, as long as the dose is equivalent and the equivalent dose calculation is documented in the medical record.
- Oral ACE inhibitors including but not limited to perindopril and lisinopril
- Oral β-blockers including but not limited to carvedilol and atenolol
- Angiotensin-receptor blockers including but not limited to losartan, irbesartan, valsartan, and candesartan
- Oral laxatives including but not limited to lactulose, Senokot, and Movicol
- Vitamin D and calcium supplements
- Alendronate (Fosamax) or other bisphosphonates used to treat osteoporosis/osteopenia by inhibiting osteoclasts
- Over-the-counter herbal preparations, including herbal supplements, vitamins, minerals, and homeopathic preparations, provided the patient had been on stable doses for at least 24 weeks before enrollment in this study

Other concomitant medications (e.g., vitamins or other medications excluding RNA antisense and gene therapies) may also be taken, if, in the opinion of the Investigator, they are not deemed to interfere with study procedures or the investigation of SRP-4053 in this study. Every attempt must be made to keep the dosage constant throughout the study period.

Introduction of new physiotherapy interventions during the course of the study must be avoided unless in the best interest of the patient. Should a contracture develop during the course of the study, and it is considered in the best interest of the patient to treat the contracture, then any of

the following interventions may be used to reduce the contracture. Any intervention must be clearly documented.

- Stretching exercises (passive, active, self)
- Night splints
- Contracture control devices
- Serial casting

If applicable, a patient who is ineligible for the study due to contracture severity (Exclusion Criterion 9) may be re-screened at the discretion of the Investigator when the contracture measures ≤10 degrees from plantigrade.

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

- Systemic or oral steroids for other conditions
- Investigational agents for the treatment of DMD
- Any medication with the potential to affect muscle mass, strength, and/or function, such as, but not limited to, growth hormone and PDE-5 inhibitors. As of Amendment 6, growth hormone for short stature and testosterone for delayed puberty are permitted if there has been confirmation and documentation of the endocrinologic diagnosis and necessity of treatment.
- Immunosuppressants (other than oral or systemic corticosteroids prescribed for DMD)
- Aminoglycoside antibiotics
- Statins

9.11. Treatment Compliance

Treatment compliance with scheduled weekly infusions will be documented on the case report form (CRF).

10. STUDY ASSESSMENTS

Schedules of study events for Part 1 (double-blind dose titration) and Part 2 (168-week open-label, treated patients only) are provided in Table 2, Table 3, and Table 4. In addition, a separate schedule of events for untreated patients (Part 2) is provided in Table 5.

10.1. Screening and Baseline Assessments

Written informed consent and informed assent will be obtained by the Investigator and study staff prior to initiating Screening activities. The Investigator and study staff will also review all inclusion and exclusion criteria and will review medical history, medication history, and documentation of DMD diagnosis during the Screening period.

In addition, all patients in Part 1 and all patients new to Part 2 (those amenable to exon 53 skipping and untreated patients) will undergo additional tests and procedures to confirm study eligibility prior to enrollment, according to the timing on the schedules of events (Table 2, Table 3, and Table 5, respectively). These tests and procedures are listed below. Untreated patients (those not amenable to exon 53 skipping) will undergo all the listed Screening/Baseline procedures except for skin and muscle biopsies.

- CCI [redacted]
- CCI [redacted]
- Muscle biopsy (Section 10.2.2) (Part 1 and Part 2-treated only)
- Functional testing including:
  - 6MWT (Section 10.2.1)
  - [redacted]
- CCI [redacted]
- [redacted]
- CCI [redacted]
- Immunogenicity (Section 10.3.4.3)
- PFTs (Section 10.2.3.1)
- ECG (Section 10.3.4.1)
- ECHO (Section 10.3.4.2)
- Vital signs (Section 10.3.1.1) including height and weight

- Physical examination (Section 10.3.2)
- Blood and urine samples for clinical laboratory assessments (Section 10.3.3)

CCI [redacted]

In Part 1, once all Screening and Baseline tests and procedures are performed and study eligibility is confirmed, patients will be randomized (2:1) in a blinded fashion (Section 9.9) to receive SRP-4053 or placebo. Part 1 patients will begin dosing at Week 1 (Table 2).

In Part 2, new patients amenable to exon 53 skipping will undergo Screening to determine study eligibility (Table 3). Rollover patients from Part 1 will not repeat Screening and will begin dosing (at the dose determined from Part 1) in Part 2 on Week 1 after the DSMB has reviewed Part 1 safety data, and Part 2 has been approved for initiation. Patients who complete the Part 1 Week 12 visit prior to the completion of the DSMB review will continue to receive blinded weekly infusions of SRP-4053 30 mg/kg or placebo as per their original randomization until after the DSMB review and Part 2 has been approved for initiation. During this unscheduled treatment period of continued dosing, patients will undergo safety laboratory assessments every 4 weeks and functional assessments every 12 weeks. Part 1 Week 12 assessments will have to be (re)done prior to Week 1 in Part 2 (rollover patients only) unless they have been completed within 4 weeks of the Week 1 visit in Part 2.

Treated patients in Part 2 will continue weekly dosing and scheduled assessments through Week 168 followed by a 4-week safety visit after their last on-study dose.

Untreated patients (those not amenable to exon 53 skipping) entering Part 2 will begin on Week 1 (Table 5) once confirmed for study eligibility; scheduled assessments will be conducted through Week 144.

As applicable, study assessments and procedures scheduled on the same day as investigational drug product administration must be completed prior to initiation of IV infusions, except for PK sampling per the defined time points.

To reduce variability, every effort must be made to have each patient assessed by the same clinical evaluator for each type of assessment throughout the entire study. All assessments are to be performed in the same order as listed in the Clinical Evaluator Manual and at approximately the same time of day at each visit. Study personnel will not have access to prior test results or information related to study-specific or routine patient care. Efficacy assessments will be performed in the morning prior to any other assessment performed during the same visit and cardiac assessments (ECG and ECHO) will be performed after the completion of functional testing at a consistent time at each visit. CCI [redacted]

In addition, all clinical evaluators will remain blinded to patients' Part 1 study treatment assignment after patients have rolled over to open-label treatment in Part 2 (Section 9.9.3).

10.2. Efficacy Assessments

10.2.1. Primary Efficacy Assessment: 6-Minute Walk Test

The 6MWT (ATS 2002) will be performed on 2 consecutive days during both Screening period and at Baseline for all patients in Parts 1 and 2 to determine eligibility. The 6MWT will also be

performed once on Day 1 each on Week 12 (±1 week) in Part 1, and on Weeks 12, 24, 36, 48, 72, 96, 120, 144, and 168 (treated patients only) (all ±2 weeks) in Part 2. Refer to the schedules of events for treated patients (Table 2, Table 3, and Table 4) and untreated patients (Table 5).

Patients will be asked to walk a set course of 25 meters for 6 minutes (timed) where the distance walked (in meters) will be recorded. Every effort will be made to ensure that the same trained and certified evaluator will make the same assessment on each patient throughout the study at the same approximate time of day. All information for the 6MWT assessments will be recorded in the source documentation and transferred to the CRF.

10.2.2. Primary Biological Assessment: Dystrophin Protein Levels Determined by Western Blot

Once confirmed as eligible for study participation, all patients in Part 1 and new patients in Part 2 who are amenable to exon 53 skipping will have pretreatment muscle [redacted] biopsies performed. Subsequently, all treated patients in Part 2 (rollover patients from Part 1 and those new to Part 2 amenable to exon 53 skipping) will undergo a second muscle biopsy at the Week 48 visit of Part 2. Biopsies at Week 48 must occur a) within 2 weeks after the Week 48 visit; b) after the clinical evaluation for Week 48, and c) at least 48 hours after the most recent infusion. After the biopsy procedure, study infusions must not be administered until at least 24 hours post biopsy, and the Investigator must medically clear the patient before the infusion may be given. No further muscle biopsies will be taken after the Week 48 biopsy.

Patients in Part 2 who are enrolled as the untreated group (those not amenable to exon 53 skipping) will not undergo muscle [redacted] biopsies.

The Baseline muscle biopsy will be obtained from one biceps brachii muscle and the subsequent muscle biopsy (Week 48) will be obtained from the contralateral muscle. A previously unbiopsied alternative upper arm muscle may be used if the biceps brachii has been biopsied previously. If an alternative muscle group is used, the same contralateral muscle will be biopsied at the subsequent muscle biopsy as well.

[redacted]

Results from biopsy procedures performed at central laboratories will be reviewed by the Laboratory Study Director(s) who is/are blinded to initial treatment group in Part 1 and to treatment duration (overall study).

10.2.3. Secondary Efficacy Assessments

10.2.3.1. Pulmonary Function Tests (PFTs)

Using standard spirometry procedures to measure breathing and pulmonary function, PFTs will be performed at Screening and Baseline visits for patients in both Parts 1 and 2. PFTs will also be performed in Part 1 at Week 12 (±1 week), in Part 2 at Weeks 12, 24, 36, 48, 72, 96, 120, 144, and 168 (FVC only for treated patients) (all ±2 weeks). The following will be recorded: forced vital capacity, maximum inspiratory pressure, and maximum expiratory pressure using standardized equipment provided by a central vendor. FVC%p, [redacted] will be calculated (Wilson 1984).

Refer to the schedules of events for treated patients (Table 2, Table 3, and Table 4) and untreated patients (Table 5).

CCI [redacted]

10.2.4. Secondary Biological Assessments

Dystrophin staining intensity and the percentage of dystrophin-positive fibers in muscle biopsy samples will be determined using IHC methods. Biopsy procedures and schedules are described above in Section 10.2.2 and in Table 2 (Part 1) and Table 3 (Part 2, treated patients).

In addition, patients in both Parts 1 and 2 (treated) will have exon skipping evaluated from muscle biopsy samples determined by measurement and sequence verification of exon 53-skipped mRNA.

Biopsy samples will be processed at central laboratories and reviewed by the Laboratory Study Director(s) who is/are blinded to initial treatment group in Part 1 and to treatment duration (overall study).

Untreated patients (those not amenable to exon 53 skipping) in Part 2 will not undergo a muscle biopsy and will not have dystrophin or exon skipping analyses performed.

CCI [redacted]

CCI

[redacted]

[redacted]

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CCI

[redacted]

10.3. Safety Assessments

10.3.1. Clinical Safety Assessments

10.3.1.1. Vital Signs Including Weight and Height

Vital signs (oral temperature, pulse rate, respiratory rate, blood pressure) and height and weight will be measured at the time points specified in Table 2 for Part 1, in Table 3 and Table 4 for treated patients in Part 2, and Table 5 for untreated patients in Part 2. In Part 1, patients in the treated and placebo group will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. In Part 2, the treated group will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion and the untreated group will have vital signs measured one time per visit. Vital sign assessments will be performed after patients have remained seated for 5 minutes. Pulse rate and respiratory rate will be measured over 1 minute.

Height will be obtained at Screening and Week 12 and weight will be obtained on a monthly basis (every 4 weeks) for all patients in Part 1. For treated patients, weight and height will be obtained every 4 weeks during the first 48 weeks of Part 2; thereafter, weight will be obtained every 12 weeks and height every 24 weeks until end of study (EOS). Height and weight will be obtained every 12 weeks for untreated patients during the first 48 weeks of Part 2, and every 24 weeks thereafter until EOS.

Height should be measured with shoes off and recorded in centimeters. If standing height cannot be obtained, height should be calculated using the following equation (Gauld 2004) where U is length of the ulna measured using an anthropometer or calipers, and A is patient's age in years:

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

10.3.2. Physical Examination

Physical examinations will be performed by the Investigator or qualified study staff according the schedules of events for Part 1 (Table 2) and Part 2 (Table 3 and Table 4 for treated patients; Table 5 for untreated patients). A full physical examination will include a review of general

appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, extremities, skin, lymph nodes, musculoskeletal, and neurological systems.

10.3.3. Clinical Laboratory Assessments

Routine clinical laboratory testing will occur according the schedules of events for Part 1 (Table 2) and Part 2 (Table 3 and Table 4 for treated patients; Table 5 for untreated patients). Laboratory results will be analyzed by an accredited central laboratory selected by the Sponsor (Sarepta Therapeutics). Assessments and shipment will be prepared according to the Laboratory Manual provided for the study. Specific laboratory parameters to be analyzed are presented in the subsections below.

10.3.3.1. Hematology

Hematology parameters to be analyzed include the following:

Red blood cells (RBC)	Lymphocytes
White blood cells (WBC)	Monocytes
Hemoglobin	Eosinophils
Hematocrit	Basophils
Neutrophils	Platelets

10.3.3.2. Coagulation

Coagulation parameters to be analyzed include the following:

Prothrombin time (PT)	International Normalized Ratio (INR)
Activated partial thromboplastin time (PTT)	

10.3.3.3. Serum Chemistry

Serum chemistry parameters to be analyzed include the following:

Sodium	Alkaline phosphatase
Chloride	Amylase
Potassium	Alanine aminotransferase (ALT)
Calcium	Aspartate aminotransferase (AST),
Glucose	Gamma-glutamyl transferase (GGT)
Creatinine	Lactase dehydrogenase (LDH)
Blood urea nitrogen (BUN)	C-reactive protein (CRP)
Albumin	Creatine kinase (CK)
Uric acid	Serum cystatin C
Total bilirubin	

10.3.3.4. Urinalysis

The following parameters will be analyzed:

pH	Cytology
Specific gravity	Hemoglobin
Protein	Kidney injury molecule-1 (KIM-1)
Glucose	Ketones

Any laboratory value(s) outside of the current reference range will be flagged.

10.3.3.5. Concomitant Medications and Therapies

The review of concomitant medications, changes in dosage of concomitant medications, and other concomitant therapies and procedures will occur at each visit beginning from the time the parents/patients sign written informed consent/assent. All information relating to concomitant medications and therapies will be recorded on the CRF.

10.3.4. Other Safety Assessments

10.3.4.1. Electrocardiogram (ECG)

In Part 1, a 12-lead ECG will be performed during Screening, Baseline and at Week 12 (Table 2). Rollover patients from Part 1 will have a 12-lead ECG every 12 weeks during the first 48 weeks of Part 2. Patients new to Part 2 will have a 12-lead ECG performed during Screening, Baseline and then every 12 weeks during the first 48 weeks of in Part 2 (refer to Table 3 for treated patients and Table 5 for untreated patients. Thereafter, ECGs will be performed every 24 weeks (Table 4 for treated patients and Table 5 for untreated patients) until Week 144. Twelve-lead ECGs will be performed only after the patient is positioned supine, resting, and is 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. The Investigator will review the results of the ECG report and designate the findings as normal, abnormal (clinically significant [CS]) or abnormal (not clinically significant [NCS]).

10.3.4.2. Echocardiography (ECHO)

A standard 2-dimensional (2D) ECHO will be performed at Screening and Week 12 in Part 1 (Table 2). Rollover patients from Part 1 will then have an ECHO every 24 weeks in Part 2. Patients new to Part 2 (treated and untreated) will have an ECHO at Screening and then every 24 weeks in Part 2 (Table 3 and Table 4 for treated patients, and Table 5 for untreated patients) until Week 144. All ECHOs will be reviewed and interpreted by medically qualified personnel using a central vendor according to prespecified criteria. Ejection fraction and fractional shortening will be noted. The Investigator will review the results of the ECHO report and designate the findings as normal, abnormal (CS or NCS).

10.3.4.3. Immunogenicity

Serum samples to evaluate immunogenicity will be assessed at the time points indicated in the schedules of events (Table 2, Table 3, and Table 4 for treated patients; Table 5 for untreated patients).

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 through the EOS visit (or early termination from the study) will be recorded in each individual patient's CRF. For patients who prematurely discontinue from the study (see Section 8.3), AEs will continue to be recorded until 4 weeks after the last SRP-4053 infusion for the randomized group or through the EOS visit for the untreated group.

If, at any time after the patient has completed participation in the study (see Section 8.3), the Investigator or study staff become aware of an SAE that the Investigator believes is possibly/probably or definitely related to the investigational drug product (Section 11.3.1) or is possibly/probably or definitely related to a study procedure (Section 11.3.2), then the event and any known details must be reported promptly to the Sponsor.

11.2. Definition of Adverse Events

11.2.1. Adverse Event (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 investigational drug product whether or not considered related to the investigational drug product. 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 baseline 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 based on Investigator judgment will be considered prolonged hospitalizations.

Persistent or significant disability/incapacity: An AE that results in a persistent or significant disability or substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the investigational product.

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. Classification of Adverse Events

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

11.3.1. Relationship to Investigational Drug Product

For each AE the Investigator determines 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 investigational drug product
Possibly/Probably Related:	The event could be related/is likely to be related to the investigational drug product
Definitely Related:	The event is clearly related to the investigational drug product

Adverse events that the Investigator or Sponsor considers to be possibly/probably or definitely related to the investigational drug product will be considered adverse drug reactions.

11.3.2. Relationship to Study Procedures

For each AE the Investigator determines 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 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 study procedures

11.3.3. Relationship to Underlying Disease

For each AE the Investigator determines 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 underlying disease
Possibly/Probably Related:	The event could be related/is likely to be related to underlying disease
Definitely Related:	The event is clearly related to underlying disease

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

11.3.4. Severity of Adverse Events

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

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

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

11.3.5. Outcome

All AEs will be followed for 4 weeks after the last dose of investigational drug product. Serious AEs will be followed until resolution, until the condition stabilizes, returns to baseline status, or until no further follow-up is expected. The Investigator will record all information regarding to patient outcome for each AE or SAE.

11.3.6. Action Taken Regarding the Investigational Drug Product

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

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CCI [redacted].

11.3.8. Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

11.4. Recording Adverse Events

All AEs/SAEs experienced from the time of informed consent/assent to the last follow-up visit (i.e., 4 weeks after the last dose of investigational drug product for treated patients) will be recorded within each patient's CRF. Information should include: a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to investigational product, study procedure and underlying disease; and any action taken are to 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, an AE is to be recorded as a diagnosis, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. Thus, multiple symptoms or laboratory results that are related to the same diagnosis are to be considered 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 the AE, completion of the patient's study participation, or study termination, whichever occurs first. Serious AEs will be followed until resolution or until the condition stabilizes or returns to baseline status or until no further follow up is expected.

11.5. 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.

11.6. Special Situations

11.6.1. Overdose

Currently, there is no basis for determining a clinically meaningful definition of overdose for SRP-4053. Therefore, as a preliminary criterion, any dose >10% above the assigned dose level will be considered an overdose.

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

11.6.2. 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.

11.6.3. Unblinding due to a Medical Emergency

In the event of a medical emergency wherein the knowledge of the patient's treatment assignment may influence clinical decision-making, the Investigator has the option to unblind treatment assignment (applicable to Part 1 only) 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.

11.6.4. Responsibilities of the Investigator

The responsibilities of the Investigator and his or her staff include the following:

- Monitor and record all AEs/SAEs
- Determine seriousness, severity, and relationship to investigational drug product and/or study procedure and/or underlying disease
- Determine the onset and end date of each event
- Provide initial report on all SAEs within 24 hours of knowledge to the Sponsor or designee
- Provide follow-up information on SAEs in a timely and proactive manner
- Respond to a queries regarding AEs and SAEs in a timely manner
- Ensure source documentation for all AEs/SAEs are accurate and complete

11.6.5. Responsibilities of the Sponsor

The responsibilities of the study Sponsor (Sarepta Therapeutics) include the following:

- Training of Investigator and site staff on AE definitions, safety assessments, and site obligations related to safety monitoring and reporting of AEs
- Training with regard to the accurate and legal reporting of SAEs to all applicable regulatory bodies, IRB/IEC(s), clinical trial sites, and other parties as appropriate and required within the regulated timing
- Recording of SAEs in the Safety Database
- Notification of SUSARs to sites
- Reporting of all SUSARs to regulatory authorities and IRB/IEC(s) according to regional requirements

- Annual safety reporting to regulatory authorities and IRB/IEC(s) according to regional requirements

11.7. Pharmacokinetic Assessments

11.7.1. Blood Sample Collection

In Part 1 (Table 2), blood collection for PK determination will occur at the following time points on Weeks 1, 3, 5, and 7: immediately predose, at approximately 5 to 10 minutes after completion of dosing, and then at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of dosing. At Week 12, blood samples will be obtained pre-infusion and between 5 and 10 minutes postinfusion.

In Part 2 (Table 3 and Table 4), blood samples for PK determination will be obtained from all treated patients pre-infusion and between 5 and 10 minutes postinfusion on Weeks 1, 24, 48, 96, and 144.

11.7.2. Urine Sample Collection

In Part 1 (only), urine for PK determination will be collected on a cumulative basis during the following time intervals: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, and 12 to 24 hours after the initiation of dosing.

12. STATISTICS

12.1. General Considerations

This section describes the rules, conventions, statistical analyses, and presentation of data for this study, Protocol 4053-101. Full details will be provided in the Statistical Analysis Plan (SAP) for this study.

Interim Analysis:

An interim analysis is planned and will be performed after all treated patients from Part 1 and Part 2 have completed the Week 48 muscle biopsy in Part 2 of the study. The study will be unblinded to the treatment in Part 1 in order to support the interim analysis. In addition, the muscle biopsy samples will be unblinded to treatment status and patient number. The interim analysis will include data for demographic and baseline characteristic, duration of exposure to study drug, and laboratory assessments of muscle biopsy tissue [redacted] The details of the interim analysis will be specified in the SAP.

The DSMB will conduct ongoing reviews of the safety data during the study. Administrative reviews of the efficacy results may be conducted (in a blinded fashion for Part 1 data before the interim analysis and in an unblinded fashion for Part 1 data after the interim analysis and Part 2 data) prior to or when all patients complete the Part 2 Week 48 visit, and again when the patients complete the Part 2 Week 96 visit, to assist in the planning of future studies for patients amenable to exon 53 skipping.

Final Analysis:

A final analysis of safety and efficacy will be conducted once the last patient completes the study and the resulting database is cleaned, quality assured, locked, and unblinded. Further details about the analyses to be conducted for this study will be presented in the SAP, which will be prepared and issued before database lock at the end of Part 2. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the clinical study report (CSR). All statistical analyses will be performed by or under the supervision of the Sponsor.

All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed unless explicitly stated in the SAP.

Percentages of patients with laboratory toxicities will be based on nonmissing values.

Baseline will generally be defined as the last available value before dosing for the SRP-4053-treated patients. Additional details and exceptions to this rule will be specified in the SAP.

12.2. Determination of Sample Size

Sample size for this study is based upon qualitative considerations; no formal sample size calculations will be performed. The following table provides probabilities for observing at least

1 AE within any particular dose level, for various incidence rates and sample sizes, and is applicable to Part 1 of the study.

Sample size	Incidence Rate		
	0.02	**0.10**	**0.30**
6	0.11	0.47	0.88
8	0.15	0.57	0.94
10	0.18	0.65	0.97
12	0.22	0.72	0.99
24	0.38	0.92	1.00

For example, if a rare event occurs 2% of the time, the probability that at least 1 patient experiences this event is 15% (in 8 patients) or 38% (in 24 patients) receiving SRP-4053.

12.3. Analysis Sets

Three analysis sets will be utilized with the definitions below applying to patients amenable to exon 53 skipping and patients in the untreated group (nonamenable to exon 53 skipping) as appropriate.

Safety Set: For Part 1, the safety set will include all randomized patients who receive at least one dose of study drug. For Part 2, the safety set will include all randomized patients from Part 1 and all Part 2 patients who receive any amount of investigational drug product and all untreated patients who enrolled in Part 2.

Efficacy Set: All randomized patients from Part 1 and all Part 2 patients who have at least one post baseline functional assessment.

Pharmacokinetic Set: All randomized patients from Part 1 who receive the full dose of investigational drug product and for whom there are adequate PK samples from which to estimate PK parameters.

12.4. Statistical Analysis

12.4.1. Protocol Deviations

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

12.4.2. Disposition, Demographics, and Baseline Characteristics

Disposition will be summarized for Part 1 and Part 2. The number and percentage of patients completing or prematurely discontinuing the study will be summarized by treatment group. Reasons for premature discontinuation will also be summarized.

Demographic and baseline characteristics such as age (years), height (cm), weight (kg), body mass index (kg/m^2), and genotype of selected genes (Section 10.2.6.2) will be summarized by treatment group. Demographic data will be presented in data listings.

12.4.3. Prior and Concomitant Medications

All prior and concomitant medications will be presented in data listings.

12.4.4. Medical History

Medical history will presented in data listings.

12.4.5. Dosing

The cumulative exposure to SRP-4053, total volume of drug administered (mL), the total number of infusions received, and the cumulative amount of drug received will be summarized by dose group for all treated patients. Dosing information will be provided in a data listing.

12.5. Efficacy Analysis

Efficacy endpoints are listed in Section 7.2.

All efficacy endpoints will be summarized descriptively by time point and treatment group for both Part 1 and Part 2. Change from baseline for each endpoint will also be summarized by time point and treatment group, if applicable.

The primary efficacy endpoint of change from baseline at Week 144 (Part 2) in the 6MWT will be summarized by treatment group.

The secondary efficacy endpoints will be analyzed similarly to the primary endpoint, as appropriate, based on the type of endpoints and the number of assessments during Part 2 of this study.

12.6. Pharmacodynamic Analysis

The primary biological endpoint of change from baseline at Week 48 (Part 2) in dystrophin protein levels as determined by Western blot will be analyzed based on a 1-sample permutation test.

The secondary biological endpoints will be analyzed similarly to the primary biological endpoint, as appropriate, based on the type of endpoints and the number of assessments during Part 2 of this study.

12.7. Safety Analyses

12.7.1. Safety Variables

The safety and tolerability of SRP-4053 will be assessed beginning at the start of Part 1 through the end of Part 2 by the review of:

- The type, frequency, severity, timing, and relationship to investigational drug product of AEs, SAEs, and discontinuations due to AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by primary system organ class (SOC) and preferred term (PT).
- Adverse events will be classified as treatment-emergent (TEAE) and non-emergent. An AE will be considered treatment-emergent if it occurs in the time period starting

with the initiation of the first dose of study drug and ending 28 days after the last dose of study drug for treated patients and on or after the Week 1 visit of Part 2 for untreated patients.

- Safety laboratory testing including hematology, coagulation, serum chemistry, and urinalysis
- Vital signs
- Physical examinations
- 12-lead ECGs (through Week 144)
- ECHOs (through Week 144)
- Immunogenicity

12.7.2. Safety Analysis

Safety analyses will be descriptive in nature.

In general, only TEAEs will be summarized. Nontreatment-emergent events will be recorded in the data listings. For all AE tables, the number and percentage of patients reporting AEs will be grouped using the MedDRA SOC and PT and summarized by treatment group and by dose level for the SRP-4053 group. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

Multiple occurrences of the same AE (at the preferred term level) in the same patient will be counted only once in the frequency tables. If a patient experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to investigational drug product will be used to summarize AEs by relationship and severity.

The following summary tables will be produced:

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

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

The following listings will be produced:

- Nontreatment-emergent AEs
- All TEAEs
- AEs leading to discontinuation
- SAEs

Descriptive statistics for ECGs, ECHOs, vital signs, physical examinations, and safety laboratory parameters will be generated. All safety data will be presented in the data listings. Additionally, shift and frequency tables of predefined change in abnormal values for select safety parameters will be generated.

Descriptive statistics for the anti-PMO immune response will be generated. The relationship between anti-PMO antibodies and clinical safety parameters may be assessed. If an anti-dystrophin antibody assay or other immunogenicity assays become available during the study, the analysis for these endpoints will be detailed in the SAP.

12.8. Pharmacokinetic Analyses

The PK of SRP-4053 will be determined from multiple plasma and urine samples collected serially following the first weekly doses of the dose-titration phase on Weeks 1, 3, 5, and 7 of Part 1 and from plasma samples collected at Weeks 1, 24, 48, 96, and 144 in Part 2. Individual plasma levels of SRP-4053 will be listed with the corresponding time related to investigational drug product administration and summary statistics will be generated by per-protocol time of collection. Pharmacokinetic parameters for SRP-4053 will be calculated using noncompartmental analysis for Part 1 and using population PK analysis in Part 2. It may be necessary to combine the data from Parts 1 and 2 to adequately perform the population PK analysis. Data collected on Week 12 in Part 1 will be included in the population PK analysis but not used for the noncompartmental analysis. Actual sampling times will be used in all final PK analyses. Per-protocol times will be used to calculate mean plasma concentrations for graphical displays. The PK parameters that will be determined include:

- C_{max}
- t_{max}
- AUC
- V_{ss}
- $t_{½}$
- CL
- MRT
- CL_R, Part 1 only

Pharmacokinetic data from Part 2 will be analyzed based on a population PK model using plasma concentration data and appropriate demographic and baseline characteristics.

13. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

13.1. Recording of Data

Clinical data for this study will be captured using an electronic data capture (EDC) system which will be set up and maintained by a contract research organization. The Investigator or personnel delegated by the Investigator will perform primary data collection/perform assessments based on the protocol design and capture source documentation. All required study information must be entered into the EDC system on the appropriate CRF screens according to the CRF Completion Guidelines for the study. A CRF must be completed for each patient that is enrolled. The study monitor will conduct 100% source data verification to ensure maximum data integrity. All data must be carefully entered in a timely fashion to permit meaningful interpretation and study oversight.

13.2. Quality Assurance

The CRFs will be reviewed by a clinical monitor from the Sponsor or a representative of the Sponsor 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 issues. Requests for data clarification or correction will be documented as electronic queries within the CRF 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.

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by regulatory authorities and/or IRB/IEC(s) 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, investigational product dispensing records and investigational product storage area, study facilities, and any other source documentation.

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

13.3. Retention of Study Documents

At study completion, all CRF data including queries and audit trail for an individual site will be generated and copied onto a CD-ROM 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 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities are notified.

These documents will be retained for a longer period, however, 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 will 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 will be retrieved and made available for review at the time of an audit or regulatory authority inspection.

13.4. Termination of Study or Study Site

If the Sponsor, the Investigator, the Medical Monitor, the study monitor, IRB/IEC, or appropriate regulatory officials discover conditions arising during the study that indicate the study must be halted or that the study center should be terminated, appropriate action must be taken after consultation among (at a minimum) the Sponsor, the Investigator, IRB/IEC and the Medical Monitor (Section 8.3). The Sponsor may terminate the study at any time.

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

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of the IRB/IEC or appropriate regulatory authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements consistent with 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 Council for Harmonisation (ICH) E6 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 investigational drug product to the Investigator and end the Investigator's participation in the investigation.

14. SPECIAL REQUIREMENTS AND PROCEDURES

14.1. Compliance with Ethical and Regulatory Guidelines

This study was designed and will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in conformance with ICH and GCP E6 guidance documents. This study will comply with the requirements that are enunciated in the European Clinical Trial Directive 2001/20/EC and in the United States (US) Code of Federal Regulations (CFR).

14.2. Regulatory and Independent Ethics Committee Review

This study will be conducted in full compliance with the European Clinical Trial Directive 2001/20/EC and/or 21 CFR 56. Before enrollment of patients into the study, the protocol and documents for informed assent (for patients) and informed consent (for parents/legal guardians) will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol will be presented to the same IRB/IEC and regulatory authority as the original protocol. The Investigator will promptly notify the Sponsor of any SAEs or of any other information that might affect the safe use of the investigational drug product during the study. IRB/IEC positive opinion and regulatory authority approval 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 will be retained in the study regulatory files.

14.3. Informed Consent/Assent

Written informed consent from each patient's parent(s) or legal guardian(s) and written assent from each patient for whom it is 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 European Clinical Trial Directive 2001/20/EC and/or 21 CFR 50.25.

14.4. Compliance with the Protocol

All processes and procedures defined in this protocol will be adhered to. Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed by the Investigator as crucial for the safety and well-being of that patient may be instituted for that patient only and documented as deviations. The Investigator will contact the Medical Monitor as soon as possible regarding such a deviation. These departures do not require 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. Documentation of IRB/IEC approval of any amendments must be returned to the Sponsor or designee.

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 European standards.

14.5.2. Patient Anonymity

The anonymity of participating patients will be maintained to the extent required by applicable laws and in accordance with current standards. Patients will be identified 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

The following documentation will be collected prior to study enrollment:

- Regulatory authority and IRB/IEC approval for all study materials (informed consent form, Protocol, any recruitment materials, etc.)
- Clinical laboratory normal ranges, when appropriate
- Signed Final Protocol page
- Investigator's Brochure review and acknowledgement
- A blank copy of the IRB/IEC-approved informed consent and assent documents and authorization
- A fully executed Clinical Trial Agreement and Confidentiality Agreement
- Signed Financial Disclosure Forms

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

The study files will also contain, patient accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, regulatory authority and IRB/IEC correspondence, deviations, biological sample records, and SAE and IND safety reports/Safety Alert Letters.

15.2. General Information

The Investigator should refer to the current Investigator's Brochure along with subsequent Safety Alert Letters, the relevant study manuals, 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. However, at the conclusion of this clinical study, a CSR will be prepared. In addition, a manuscript will be prepared for publication in a reputable scientific journal under the direction of Sarepta Therapeutics Inc. The Sponsor (Sarepta Therapeutics) and the Investigators intend to 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, on clinicaltrialregister.eu, and on any national registry, as appropriate. After completion of the study, results will be disseminated through these registries.

15.4. Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the investigational product, the Investigator, clinical site pharmacist or pharmacy designee must contact the Sponsor or designated contract research organization (CRO).

16. LIST OF REFERENCES

American Academy of Orthopedic Surgeons (AAOS). Pediatric Outcomes Questionnaire. Pediatric Orthopaedic Society of North America, American Academy of Pediatrics, Shriner's Hospitals, eds. Version 2.0, August 2005. Available from: http://www.aaos.org/uploadedFiles/PreProduction/Quality/About_Quality/outcomes/Pediatric.pdf. Accessed March 2016.

Amor CJ, Spaeth MC, Chafey DH, Gogola GR. Use of the Pediatric Outcomes Data Collection Instrument to evaluate functional outcomes in arthrogryposis. J Pediatr Orthop. 2011;31(3):293-6.

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

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.

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

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

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

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

Centers for Disease Control, Prevention. Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years - four states, 2007. MMWR Morb Mortal Wkly Rep. 2009;58(40):1119-22.

Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet. 2011;378(9791):595-605.

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

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

Flanigan KM, Ceco E, Lamar KM, et al. LTBP4 genotype predicts age of ambulatory loss in Duchenne muscular dystrophy. Ann Neurol. 2013;73(4):481-8.

Gauld LM, Kappers J, Carlin JB, et al. Height prediction from ulna length. Dev Med Child Neurol. 2004;46(7):475-80.

CCI

Kinali M, Arechavala-Gomeza V, Feng L, et al. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. Lancet Neurol. 2009;8(10):918-28.

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

CCI

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

CCI

CCI

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

Mazzone E, Martinelli D, Berardinelli A, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2010;20(11):712-6.

McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test in Duchenne/Becker muscular dystrophy: longitudinal observations. Muscle Nerve. 2010;42(6):966-74.

Pegoraro E, Hoffman EP, Piva L, et al. SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology. 2011;76(3):219-26.

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

Uzark K, King E, Cripe L, et al. Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. Pediatrics. 2012;130(6):e1559-66.

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