# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **DRUG (CODE NAME):** | SRP-4045 |
| **PROTOCOL NUMBER:** | 4045-101 |
| **PROTOCOL TITLE:** | A Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study Followed by an Open-Label Safety and Efficacy Evaluation of SRP-4045 in Advanced-Stage Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping |
| **IND NO.** | [redacted] |
| **STUDY PHASE:** | 1 |
| **SPONSOR:** | Sarepta Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 |
| **CURRENT VERSION (DATE):** | Version 4.0 (Amendment 3), 29 March 2018 |
| **PRIOR VERSION DATE:** | Version 3.1 (Amendment 2), 02 May 2017<br>Version 2 (Amendment 1), 22 July 2015<br>Version 1, 12 June 2014 |

[redacted]

# SIGNATURE PAGE FOR SPONSOR

| | |
|---|---|
| **Protocol Title:** | A Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study Followed by an Open-Label Safety and Efficacy Evaluation of SRP-4045 in Advanced-Stage Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping |
| **Study No:** | 4045-101 (Amendment 3) |
| **Current Version (Date):** | 29 March 2018 |

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, principles of International Council for Harmonization (ICH), Good Clinical Practice (GCP) E6, and/or the European Clinical Trial Directive 2001/20/EC.

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

[redacted], MD, PhD Date

PPD

[redacted], MD Date

# INVESTIGATOR'S AGREEMENT

I have read Protocol No. 4045-101 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 | PPD<br>Telephone: PPD<br>Mobile: PPD<br>PPD |

# 1. SYNOPSIS

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | SRP-4045 Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>SRP-4045 |

**TITLE:** A Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study Followed by an Open-Label Safety and Efficacy Evaluation of SRP-4045 in Advanced-Stage Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping

**PROTOCOL NUMBER:** 4045-101

**PHASE OF STUDY:** Phase 1

**INVESTIGATOR STUDY SITES:** This multi-center study will be conducted at approximately 4 sites in the United States.

**OBJECTIVES:**

Primary objective:

- To evaluate the safety and tolerability of 4 escalating intravenous (IV) doses (4, 10, 20, and 30 mg/kg) of SRP-4045 administered once weekly for at least 2 weeks per dose level as compared to placebo

Secondary objective:

- To determine the pharmacokinetic (PK) profile of 4 escalating IV doses of SRP-4045

CCI [redacted]

**METHODOLOGY:**

This is a first-in-human, multi-center, randomized, double-blind, placebo-controlled, dose-titration study designed to assess the safety, tolerability, and PK of once-weekly IV infusions of SRP-4045 in advanced-stage patients with genotypically confirmed Duchenne muscular dystrophy (DMD) characterized by deletions amenable to exon 45 skipping (eg, exons 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55). This study will evaluate 4 ascending dose levels of SRP-4045 (4, 10, 20, and 30 mg/kg administered weekly for a minimum of 2 weeks per level) compared to placebo over approximately 12 weeks of a double-blind dose-titration period. The double-blind dose-titration period will be followed by an open-label extension period evaluating the safety and efficacy of SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration) administered weekly through Week 144. After completing the open-label extension period, eligible patients may enter a planned long-term extension (LTE) study for extended treatment. All activities for these subjects will be outlined in a LTE study protocol.

Screening Period

Patients will be evaluated for inclusion during a Screening period of up to approximately 4 weeks.

Baseline/Week 1

Eligible patients who have out-of-frame deletions that may be corrected by skipping exon 45 will be randomized to receive once-weekly IV infusions of SRP-4045 or placebo.

[redacted]

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | SRP-4045 Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>SRP-4045 |

Double-Blind Dose Titration with Open-Label Extension (144 weeks)

*Dosing*

Twelve patients will be randomized (2:1) in double-blind fashion to receive SRP-4045 (n=8) or placebo (n=4). Patients will receive a once-weekly IV infusion of SRP-4045 or placebo at escalating dose levels, each for at least 2 weeks: 4 mg/kg at Weeks 1-2; 10 mg/kg at Weeks 3-4; 20 mg/kg at Weeks 5-6; and 30 mg/kg beginning at Week 7. During the dose titration period of the study, dosing will be interrupted or halted if specific predefined stopping criteria are met, or if interruption is otherwise warranted at the discretion of the Sponsor or Investigator. Once the last patient has received 2 infusions at 30 mg/kg (Week 8), an independent Data Safety Monitoring Board (DSMB) will review cumulative safety data. Review by the DSMB is necessary for advising the Sponsor about whether the safety data allow for longer-term dosing with SRP-4045. Patients will continue to receive their randomized treatment (SRP-4045 or placebo) in a blinded fashion until the DSMB review is complete. Based on the results of this review, the Sponsor will determine whether to roll over the patients into the open-label extension period. During the open-label extension, patients will receive SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration) administered weekly.

*Assessments*

Patients will undergo routine safety evaluations. Adverse events (AEs) and concomitant medications will be monitored and documented continually over the course of the study.

CCI [redacted] Plasma samples for serial PK determination will be collected at Baseline/Week 1 and Weeks 3, 5, 7, and 60. Urine samples for serial PK determination will be collected at Baseline/Week 1 and Weeks 3, 5, 7, and 12.

In addition to serial PK, standard population PK parameters will be estimated from additional plasma samples taken over the course of 144 weeks.

CCI [redacted] An electrocardiogram (ECG) will be performed at Baseline/Week 1, Week 7, Week 12, and then every 12 weeks. An echocardiogram (ECHO) will be performed at Week 12, and then every 24 weeks. Clinical laboratory assessments will be performed at Baseline/Week 1, Weeks 2-9, and Week 12, then every 4 weeks to Week 36, and then every 12 weeks. Vital signs will be assessed weekly pre- and post-infusion. Height will be assessed every 12 weeks. Weight will be assessed at Baseline/Week 1, and then every 4 weeks. A full physical examination will be conducted at Baseline/Week 1, Week 4, Week 12, Week 24, and then every 24 weeks. A brief physical examination will be conducted every 4 weeks (except at times of a full physical examination) to Week 36, and then every 24 weeks. Patients will undergo additional physical examinations, ECGs, clinical laboratory assessments and CCI [redacted] during the first 8 weeks of open-label treatment.

**DURATION OF STUDY:**

Screening Period: up to approximately 4 weeks

Double-Blind Dose-Titration with Open-Label Extension: up to144 weeks

Post-treatment Follow-Up Period: approximately 4 weeks

Total duration of patient participation: approximately 152 weeks

[redacted]

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | SRP-4045 Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>SRP-4045 |

**NUMBER OF PATIENTS:**

12 patients (8 SRP-4045 + 4 placebo)

**INCLUSION CRITERIA:**

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

1. Male aged 7 to 21, inclusive.
2. Established clinical diagnosis of DMD with a deletion amenable to exon 45 skipping (eg, deletions of exons 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55) as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing.
3. Stable cardiac and pulmonary function that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study
4. Non-ambulatory, or incapable of walking ≥300 meters on the 6-Minute Walk Test (6MWT).
5. On a stable dose of oral corticosteroids for at least 24 weeks prior to study drug administration and the dose or dose equivalent is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study, OR has not received corticosteroids for at least 24 weeks prior to study drug administration and does not expect to start corticosteroids throughout the study.
6. Patients who are post-pubertal and sexually active must agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (eg, oral contraceptive).
7. Able to understand and comply with all study requirements, in the Investigator's opinion, or if under the age of 18 years, must have (a) parent(s) or legal guardian(s) who is/are able to understand and comply with all the study requirements.
8. Willing to provide informed consent to participate in the study, or if under the age of 18 years, willing to provide informed assent, if applicable, and has (a) parent(s) or legal guardian(s) who is/are willing to provide written informed consent for the patient to participate in the study.

**EXCLUSION CRITERIA:**

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

1. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks prior to Baseline/Week 1 that might in the Investigator's judgment have an effect on muscle strength or function (eg, growth hormone, anabolic steroids). (Current growth hormone treatment for short stature will be allowed if medically indicated.)
2. Current or previous treatment with the experimental agents SMT C1100 (BMN-195) or PRO045 at any time.

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | SRP-4045 Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>SRP-4045 |

3. Use of other RNA antisense or gene therapy agents.
4. Current or previous treatment with any other experimental treatment (other than deflazacort) within 12 weeks prior to Baseline/Week 1 or participation in any other interventional clinical trial within 12 weeks prior to Baseline/Week 1.
5. Use of any aminoglycoside antibiotic or statin within 12 weeks prior to Baseline/Week 1 or anticipated need for an aminoglycoside antibiotic or statin during the study.
6. Initiation or change of dosing (except for modifications to accommodate changes in weight) within 12 weeks prior to Baseline/Week 1 and/or anticipated need for a change in dosing (except for modifications to accommodate changes in weight) during the study for any of the following: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β-blockers, potassium.
7. Initiation or change of dosing within 12 weeks prior to Baseline/Week 1 and/or anticipated need for a change in dosing during the study for over-the-counter preparations such as herbal/non-herbal supplements, vitamins, minerals, and homeopathic preparations.
8. Left ventricular ejection fraction (LVEF) <40% on the Screening ECHO, and/or QTcF ≥450 msec on the Screening ECG.
9. Forced vital capacity (FVC) <50% of predicted value at Screening and/or Baseline/Week 1, and/or requirement for nocturnal ventilation.
10. Major surgery within 3 months prior to Baseline/Week 1 or planned surgery for any time during this study.
11. Presence of other clinically significant illness including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
12. Any other condition that, in the Investigator's opinion, could interfere with the patient's participation in the study.

**DOSE/ROUTE/REGIMEN:**

SRP-4045 (4, 10, 20, and 30 mg/kg) will be administered as an IV infusion over approximately 35-60 minutes once a week.

**REFERENCE TREATMENT:**

Patients randomized to placebo will receive normal saline as an IV infusion over approximately 35-60 minutes once a week until the open-label extension.

**CRITERIA FOR EVALUATION:**

The primary study endpoint is assessment of the safety of SRP-4045 during the double-blind dose-titration period according to the following:

- Incidence of AEs
- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations (PE)
- Clinically significant worsening of ECGs and ECHO

The secondary study endpoint is to determine the PK profile of SRP-4045 during the double-blind dose-titration period (see below).

[redacted]

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | SRP-4045 Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>SRP-4045 |

CCI [redacted]

**Pharmacokinetics:**

Serial plasma PK sampling will be performed at Baseline/Week 1 and Weeks 3, 5, 7, and 60 at the following time points: immediately pre-infusion, at approximately 5 to 10 minutes after completion of infusion, and at 1, 1.5, 2, 4, 6, 8 12, 16, and 24 hours after completion of infusion. CCI [redacted] The following PK parameters will be determined:

- 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 ($CL_R$)

CCI [redacted]

**SAMPLE SIZE:**

The sample size for this study is based upon qualitative considerations; no formal sample size calculations were performed. The selected sample size is considered sufficient to provide initial safety evaluation of SRP-4045 and to provide adequate data to allow for estimation of PK parameters.

**STATISTICAL METHODS:**

Baseline characteristics, safety, and tolerability will be based upon the review of individual values and summary statistics. Incidence of treatment-emergent adverse events (TEAEs) will be tabulated by

| NAME OF COMPANY | NAME OF FINISHED PRODUCT |
|---|---|
| Sarepta Therapeutics, Inc.<br>Cambridge, MA 02142 USA<br>Phone: +1-617-274-4000 | SRP-4045 Injection<br><br>**NAME OF ACTIVE INGREDIENT**<br>SRP-4045 |

counts and percentages. Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by dose and treatment group (SRP-4045 or placebo) showing subject counts and percentages.

**Safety Analyses:**

TEAEs will be summarized by system organ class (SOC) and preferred term (PT). Non-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 Medical Dictionary for Regulatory Activities (MedDRA) body system and PT. Multiple occurrences of the same AE (at the PT 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 ECG, ECHO, vital signs, biomarkers, and safety laboratory parameters will be displayed. All safety data will be presented in data listings.

**Pharmacokinetic Analyses:**

Pharmacokinetic parameters of SRP-4045 will be determined from analyses of multiple plasma and urine samples collected for each dose level. Individual plasma levels of SRP-4045 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. PK parameters for SRP-4045 will be calculated using non-compartmental 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 following PK parameters will be determined:

- $C_{max}$
- $T_{max}$
- AUC
- $V_{ss}$
- $t_{½}$
- CL
- MRT
- $CL_R$

CCI [redacted] Available patient characteristics (demographics, laboratory variables, genotypes, concomitant medications, etc) will be tested as potential covariates affecting PK parameters.

CCI [redacted]

[redacted]

# 2. SCHEDULE OF EVENTS

The schedule of study events is provided in Table 2.

**Table 2: Schedule of Events: Double-Blind Dose Titration with Open-Label Extension**

| Week | SCRN -4 TO 0 | BL/1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Window | ≤4 Weeks | ±1 day | | | | | | | | | | | |
| Informed consent/assent | X | | | | | | | | | | | | |
| Inclusion/exclusion Criteria | X | | | | | | | | | | | | |
| Medical History [a] | X | | | | | | | | | | | | |
| Document DMD Diagnosis | X | | | | | | | | | | | | |
| Whole Blood (Genotype/SNP) [b] | X | | | | | | | | | | | | |
| 6MWT | X | | | | | | | | | | | | |
| Full Physical Examination [c] | X | X | | | X | | | | | | | | X |
| Brief Physical Examination [d] | | | | | | | | | X | | | | |
| Vital signs [e] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height [f] | X | | | | | | | | | | | | X |
| Weight | X | X | | | X | | | | X | | | | X |
| CCI | | | | | | | | | | | | | |
| Confirm eligibility | | X | | | | | | | | | | | |
| Randomization [g] | | X | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | |
| 12-lead ECG [h] | X | X | | | | | | X | | | | | X |
| ECHO [h] | X | | | | | | | | | | | | X |
| Clinical laboratory | X[i] | X | X | X | X | X | X | X | X | X | | | X |
| CCI | | | | | | | | | | | | | |
| Plasma/urine for PK [k] | | X | | X | | X | | X | | | | | X |
| Dosing [l] | | 4[l] mg/kg | 4 mg/kg | 10 mg/kg | 10 mg/kg | 20 mg/kg | 20 mg/kg | 30 mg/kg | 30 mg/kg | 30 mg/kg | 30 mg/kg | 30 mg/kg | 30 mg/kg |
| | | Weekly infusions of the above doses or placebo beginning at Baseline/Week 1 | | | | | | | | | | | |
| DSMB [m] | | | | | | | | | | ------X------ | | | |
| Concomitant medications | Continuous | | | | | | | | | | | | |
| AE monitoring | Continuous | | | | | | | | | | | | |

[redacted]

6MWT=6-minute walk test; AE=adverse event; BL=Baseline; DMD=Duchenne muscular dystrophy; DSMB=Data Safety Monitoring Board; ECG=electrocardiogram; ECHO=echocardiogram; CCI

[a] Includes medication and physiotherapeutic intervention history.
[b] Patients may start dosing based on local genotyping results provided that these results fulfil the required inclusion criteria; however, all patients must undergo genetic testing to confirm the exon 45 skippable mutation and to assess genetic CCI of disease severity.
[c] Complete physical examination to include review of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems.
[d] Brief physical examinations will include examination of general appearance, HEENT, heart, chest, abdomen, and skin.
[e] Vital signs include blood pressure, pulse, respiration rate, and temperature. For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.
[f] Height and ulnar length taken at Screening and Week 12. If patient is unable to stand, then height can be calculated using ulnar length as described in Section 10.3.1.
[g] Randomization (8 SRP-4045 + 4 placebo) will occur at Baseline/Week 1 after confirming all eligibility criteria prior to first dose.
[h] 12-lead ECGs and ECHOs will be performed at a consistent time of day throughout the study.
[i] Safety laboratory assessments must be performed within 2 weeks prior to the Baseline/Week 1 visit, and results must be reviewed prior to dosing. If Screening safety laboratory samples were collected more than 2 weeks prior to the Baseline/Week 1 visit, samples must be collected again and results must be reviewed before patients may be dosed at Baseline/Week 1.
CCI
[k] Serial plasma PK sampling will be performed during the double-blind dose-titration period at Baseline/Week 1 and Weeks 3, 5, and 7 at the following time points at the first weekly dose for each dose level: immediately pre-infusion, approximately 5 to 10 minutes after completion of infusion, and at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of infusion. At Weeks 1, 3, 5, 7, and 12, urine for PK sampling will be collected, on a cumulative basis, during the following time intervals based on start of infusion: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. In addition, at Week 7, urine will also be collected 24 to 36 hours after the start of infusion. Patients will be asked to void their bladders prior to the start infusion.
CCI
[l] Randomized patients will be dose-escalated every 2 weeks to receive weekly infusions of SRP-4045 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 to 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 are to 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.
[m] DSMB safety data evaluation begins once the last patient has received 2 infusions at 30 mg/kg (Week 8). Patients shall continue to receive double-blind treatment (SRP-4045 30 mg/kg or placebo) until the DSMB completes its review. Based on the results of this review, the Sponsor will determine whether to roll over patients into the open-label extension period.

**Table 2: Schedule of Events: Double-Blind Dose Titration with Open-Label Extension, continued**

| Week | 13-15 | 16 | 17-19 | 20 | 21-23 | 24 | 25-27 | 28 | 29-31 | 32 | 33-35 | 36 | 37-47 | 48 | 49-59 | 60 | 61-71 | 72 | 73-83 | 84 | 85-95 | 96 | 97-107 | 108 | 109-119 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Window | After transition to open-label SRP-4045: ±3 days such that no 2 infusions are less than 60 hours apart | | | | | | | | | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 12-lead ECG | | | | | | X | | | | | | X | | X | | X | | X | | X | | X | | X | | X |
| ECHO | | | | | | | | | | | | X | | | | X | | | | X | | | | X | | |
| Full Physical Exam [c] | | | | | | X | | | | | | | | X | | | | X | | | | X | | | | X |
| Brief Physical Examination [d] | | X | | X | | | | X | | X | | X | | | | X | | | | X | | | | X | | |
| Height and ulnar length [e] | | | | | | X | | | | | | X | | X | | X | | X | | X | | X | | X | | X |
| Weight | | X | | X | | X | | X | | X | | X | Once every 4 weeks | | | | | | | | | | | | | |
| Vital signs [f] | Weekly Pre- and Post-Infusion | | | | | | | | | | | | | | | | | | | | | | | | | |
| Safety Lab Assessments [g] | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| CCI | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PK [h] | | | | | | X | | | | | | X | | X | | X | | X | | X | | X | | X | | X |
| Dosing [i,j] | Weekly Infusions: Patients to receive placebo or SRP-4045 as randomized until DSMB review and Sponsor determination of weekly open-label dose level | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | Continuous | | | | | | | | | | | | | | | | | | | | | | | | | |
| AE monitoring | Continuous | | | | | | | | | | | | | | | | | | | | | | | | | |

AE=adverse event; DSMB=Data Safety Monitoring Board; ECG=electrocardiogram; ECHO=echocardiogram; CCI

[redacted]

[a] A safety follow-up visit will occur approximately 4 weeks after the last study infusion at the End of Study (EoS) or for Early Termination (ET).

[redacted]

CCI [redacted]

[c] Full physical examination to include review of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems.

[d] Brief physical examination to include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

[e] Height and ulnar length to be collected. If patient is unable to stand, then height can be calculated using ulnar length as described in Section 10.3.1.

[f] Vital signs include blood pressure, heart rate, respiration rate, and oral temperature. For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after 48 weeks of open-label treatment, the Investigator has discretion to collect post-infusion vital signs at 5 and 30 minutes.

[g] Before patients may begin dosing in the open-label extension period, safety laboratory assessments must be performed within 2 weeks prior to first dose. If safety laboratory samples were collected more than 2 weeks prior to the first open-label extension visit, samples must be collected again and results must be reviewed before dosing.

[h] At Weeks 24, 36, 48, 72, 84, 96, 108, and 120, CCI [redacted] Additional samples will also be taken at Weeks 24, 48, 72, 96, and 120 approximately 2-4 hours after completion of the infusion. At Week 60, plasma samples for serial PK will be obtained immediately pre-infusion, approximately 5 to 10 minutes after completion of the infusion, and approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of the infusion.

[i] All patients will receive open-label treatment with SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration) administered weekly. Infusions are to be given according to instructions in the Pharmacy Manual. Note that an implanted venous access port may be inserted for treatment administration at the discretion of the Investigator. Patients are to be closely monitored for at least 1 hour following the completion of all infusions. If the patient has not experienced an infusion reaction after 48 weeks of open-label treatment, the Investigator has discretion to reduce the post-infusion observation period to 30 minutes.

[j] Home infusions may take place 3 out of every 4 weeks, with the fourth week conducted at the study site. This schedule is intended to reduce study burden while maintaining ongoing in-person surveillance by the study site. Detailed instructions for in-home dosing will be provided in a separate manual to the visiting nurse.

**Table 2: Schedule of Events: Double-Blind Dose Titration with Open-Label Extension, continued**

| Week | 121-131 | 132 | 133-143 | 144 | F/U EoS/ ET [a] |
|---|---|---|---|---|---|
| Visit Window | After transition to open-label SRP-4045: ±3 days such that no 2 infusions are less than 60 hours apart | | | | |
| CCI | | | | | |
| 12-lead ECG | | X | | X | |
| ECHO | | X | | | |
| Full Physical Exam [c] | | | | X | X |
| Brief Physical Examination [d] | | X | | | |
| Height and ulnar length [e] | | X | | X | X |
| Weight | Once every 4 weeks | | | | X |
| Vital signs [f] | Weekly Pre- and Post-Infusion | | | | X |
| Safety Lab Assessments [g] | | X | | X | X |
| CCI | | | | | |
| Dosing [i,j] | Weekly Infusions: Patients to receive placebo or SRP-4045 as randomized until DSMB review and Sponsor determination of weekly open-label dose level | | | | |
| Concomitant medications | Continuous | | | | |
| AE monitoring | Continuous | | | | |

AE=adverse event; DSMB=Data Safety Monitoring Board; ECG=electrocardiogram; ECHO=echocardiogram; EoS=end of study; ET=early termination; F/U=follow-up; CCI [redacted]

[a] Follow-up (F/U) for End of Study (EoS) is applicable for patients who complete Study 4045-101, but who do not choose to participate in the long-term extension (LTE) study. A safety follow-up visit will occur approximately 4 weeks after the last study infusion at the EoS or for Early Termination (ET). F/U ET is required for patients who discontinue prematurely from Study 4045-101. Patients who complete Study 4045-101 per protocol and who roll over to the LTE study will not require a F/U visit for Study 4045-101.

CCI [redacted]

[c] Full physical examination to include review of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems.

[d] Brief physical examination to include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

[e] Height and ulnar length to be collected. If patient is unable to stand, then height can be calculated using ulnar length as described in Section 10.3.1.

[f] Vital signs include blood pressure, heart rate, respiration rate, and oral temperature. For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. If the patient has not experienced an infusion reaction after 48 weeks of open-label treatment, the Investigator has discretion to collect post-infusion vital signs at 5 and 30 minutes.

[redacted]

[g] Before patients may begin dosing in the open-label extension period, safety laboratory assessments must be performed within 2 weeks prior to first dose. If safety laboratory samples were collected more than 2 weeks prior to the first open-label extension visit, samples must be collected again and results must be reviewed before dosing.

CCI [redacted]

[i] All patients will receive open-label treatment with SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration) administered weekly. Infusions are to be given according to instructions in the Pharmacy Manual. Note that an implanted venous access port may be inserted for treatment administration at the discretion of the Investigator. Patients are to be closely monitored for at least 1 hour following the completion of all infusions. If the patient has not experienced an infusion reaction after 48 weeks of open-label treatment, the Investigator has discretion to reduce the post-infusion observation period to 30 minutes.

[j] Home infusions may take place 3 out of every 4 weeks, with the fourth week conducted at the study site. This schedule is intended to reduce study burden while maintaining ongoing in-person surveillance by the study site. Detailed instructions for in-home dosing will be provided in a separate manual to the visiting nurse.

[redacted]

**Table 3: Schedule of Events: Introduction of Open-Label Treatment**

Note: Open-label treatment may commence once the DSMB has reviewed double-blind dose-titration safety data and the Sponsor's decision has been made to proceed. The assessments in Table 3 will occur during the first 8 weeks of the open-label study period and are in addition to the assessments in Table 2. Duplicate assessments at the same study visit should not be performed.

| | OPEN LABEL INTRODUCTION | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Study week will vary for each patient such that the Open Label Week 1 will be the patient's next scheduled visit after the DSMB review and Sponsor determination of weekly open-label dose level | | | | | | | |
| **Open Label Week** | **OL W1** | **OL W2** | **OL W3** | **OL W4** | **OL W5** | **OL W6** | **OL W7** | **OL W8** |
| Full Physical Examination [a] | X | | | X | | | | |
| Brief Physical Examination [b] | | | | | | | | X |
| 12-lead ECG | X | | X | | | | | |
| Clinical Laboratory Assessments | X[c] | X | X | X | X | X | X | X |
| CCI | | | | | | | | |

DSMB=Data Safety Monitoring Board; ECG=electrocardiogram; OL=open label; W=week.

[a] Full physical examination to include review of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems.

[b] Brief physical examination will include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

[c] Before patients may begin open-label treatment, safety laboratory assessments must be performed within 2 weeks prior to first dose. If safety laboratory samples were collected more than 2 weeks prior to the first open-label extension visit, samples must be collected again and results must be reviewed before dosing.

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

## TABLE OF CONTENTS



[redacted]

[redacted]

[redacted]

## LIST OF TABLES



## LIST OF FIGURES

# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

**Table 4: List of Abbreviations and Definitions**

| Abbreviation or term | Definition |
|---|---|
| 2D | 2-dimensional |
| 6MWT | 6-Minute Walk Test |
| ACE | angiotensin-converting enzyme |
| AE(s) | adverse event |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| ARB | angiotensin receptor blocker |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BMD | Becker muscular dystrophy |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| °C | degrees Celsius |
| CAP | College of American Pathologists |
| CD | compact disc |
| CFR | Code of Federal Regulations |
| CK | creatine kinase |
| CLIA | Clinical Laboratory Improvement Amendments |
| CL | total clearance |
| $CL_R$ | urinary clearance |
| $C_{max}$ | maximum plasma concentration |
| CRF | case report form |
| CRO | contract research organization |
| CRP | C-reactive protein |
| CSR | clinical study report |
| DMD | Duchenne muscular dystrophy |
| DNA | deoxyribonucleic acid |
| DSMB | Data Safety Monitoring Board |

**Table 4: List of Abbreviations and Definitions**

| Abbreviation or term | Definition |
|---|---|
| ECG | electrocardiogram |
| ECHO | echocardiogram/echocardiography |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EF | ejection fraction |
| EoS | end of study |
| ET | early termination |
| FDA | Food and Drug Administration |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyl transferase |
| HEENT | head, eyes, ears, nose, and throat |
| hGH | human growth hormone |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IP | investigational product |
| IRB | Institutional Review Board |
| IV | intravenous |
| KIM-1 | kidney injury molecule 1 |
| LDH | lactase dehydrogenase |
| CCI [redacted] | |
| LTE | long-term extension |
| LVEF | left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| CCI [redacted] | |
| MLPA | multiplex ligation-dependent probe amplification |

[redacted]

**Table 4: List of Abbreviations and Definitions**

| Abbreviation or term | Definition |
|---|---|
| MMWR | Morbidity and Mortality Weekly Report |
| mRNA | messenger RNA |
| MRT | mean residence time |
| NOAEL | no observable adverse effect level |
| PBS | phosphate-buffered saline |
| PDE-5 | phosphodiesterase type 5 |
| PE | physical examination |
| CCI | |
| PI | Principal Investigator |
| PK | pharmacokinetic(s) |
| PMO | phosphorodiamidate morpholino oligomer |
| CCI | |
| PT | preferred term |
| RNA | ribonucleic acid |
| RBC | red blood cell |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| Sarepta | Sarepta Therapeutics, Inc. |
| SNP | single nucleotide polymorphism |
| SOC | system organ class or standard of care |
| CCI | |
| SRP-4045 | investigational drug product for exon 45 skipping |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{½}$ | elimination half-life |
| TEAE | treatment-emergent AE |
| $T_{max}$ | time to maximum plasma concentration |
| $V_{ss}$ | volume of distribution at steady-state |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell (count) |

[redacted]

# 5. INTRODUCTION

CCI

[redacted]

CCI

[redacted]

## 5.4. Rationale for the Current Study

The rationale of the current study is to assess the safety and tolerability of SRP-4045 for the first time in a clinical setting. In addition, this study will evaluate PK of SRP-4045, as well as assess CCI [redacted] efficacy endpoints in DMD patients amenable to skipping exon 45 and will be used to establish the dose for use in further clinical trials with SRP-4045.

[redacted]

# 6. STUDY OBJECTIVES

## 6.1. Primary Objective

- To evaluate the safety and tolerability of 4 escalating IV doses (4, 10, 20, and 30 mg/kg) of SRP-4045 administered once weekly for at least 2 weeks per dose level as compared to placebo.

## 6.2. Secondary Objective

- To determine the PK profile of 4 escalating doses of SRP-4045.

CCI [redacted]

# 7. INVESTIGATIONAL PLAN

## 7.1. Overall Study Design

This is a first-in-human, multicenter, multiple-dose study designed to assess the safety, tolerability, and PK of once-weekly IV infusions of SRP-4045 in ambulatory patients with genotypically confirmed DMD characterized by deletions amenable to exon 45 skipping (eg, deletions of exons 12-44, 18-44, 44, 46-47, 46-48, 46-49,46-51, 46-53, or 46-55). This study will be conducted at approximately 4 study centers as a randomized, double-blind, placebo-controlled, dose-titration evaluation of 4 dose levels of SRP-4045 (4, 10, 20, and 30 mg/kg administered weekly for a minimum of 2 weeks per level) compared to placebo over approximately 12 weeks. The double-blind dose-titration period will be followed by an open-label extension period evaluating the safety and efficacy of SRP-4045 30 mg/kg (or the highest tolerated dose as determined during the dose titration) administered weekly through Week 144. After completing the open-label extension period, eligible patients may enter a planned long-term extension (LTE) study for extended treatment. All activities for these subjects will be outlined in a LTE study protocol.

The total study duration will be approximately 152 weeks, encompassing a Screening period (up to approximately 4 weeks), a double-blind dose-titration period followed by an open-label extension (up to 144 weeks), and a 4-week post-treatment safety follow-up. Follow-up for end of study is applicable for patients who complete Study 4045-101, but who do not choose to participate in the LTE study. A safety follow-up visit will occur approximately 4 weeks after the last study infusion at the end of study or for early termination. Follow-up for early termination is required for patients who discontinue prematurely from Study 4045-101. Patients who complete Study 4045-101 per protocol and who roll over to the LTE study will not require a follow-up visit for Study 4045-101.

Non-ambulatory DMD patients or DMD patients unable to walk 300 meters or more on the 6MWT will participate in an up to approximately 4-week Screening period to ensure eligibility prior to randomization to SRP-4045 or placebo. An echocardiogram (ECHO) and electrocardiogram (ECG) will also occur during Screening. A DNA sample to confirm the genetic deletion and CCI [redacted], and blood and urine samples for clinical laboratory testing will be taken. CCI [redacted] A full physical examination will be conducted during Screening. Eligible patients who have out-of-frame deletions that may be corrected by skipping exon 45 will be randomized to receive once-weekly IV infusions of SRP-4045 or placebo. Twelve patients will be randomized (2:1) in double-blinded fashion to receive SRP-4045 (n=8) or placebo (n=4). Patients will receive a once-weekly IV infusion of SRP-4045 or placebo at escalating dose levels, each for at least 2 weeks: 4 mg/kg at Weeks 1 to 2; 10 mg/kg at Weeks 3 to 4; 20 mg/kg at Weeks 5 to 6; and 30 mg/kg beginning at Week 7. Refer to Section 7.2.3 for specific details regarding spacing of initial doses between patients during dose titration. During the dose titration period of the study, dosing will be interrupted or halted if specific predefined stopping criteria are met or if otherwise

warranted at the discretion of the Sponsor or Investigator. Once the last patient has received 2 infusions at 30 mg/kg (Week 8), an independent Data Safety Monitoring Board (DSMB) will review cumulative safety data. Review by the DSMB is necessary for advising the Sponsor about whether the safety data allow for longer-term dosing with SRP-4045. Patients will continue to receive their randomized treatment (SRP-4045 or placebo) in a blinded fashion until the DSMB review is complete. Based on the results of this review, the Sponsor will determine whether to roll over patients into the open-label extension period. During the open-label extension, patients will receive SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration) weekly.

Patients will undergo routine safety evaluations. Adverse events (AEs) and concomitant medications will be monitored and documented continually over the course of the study.

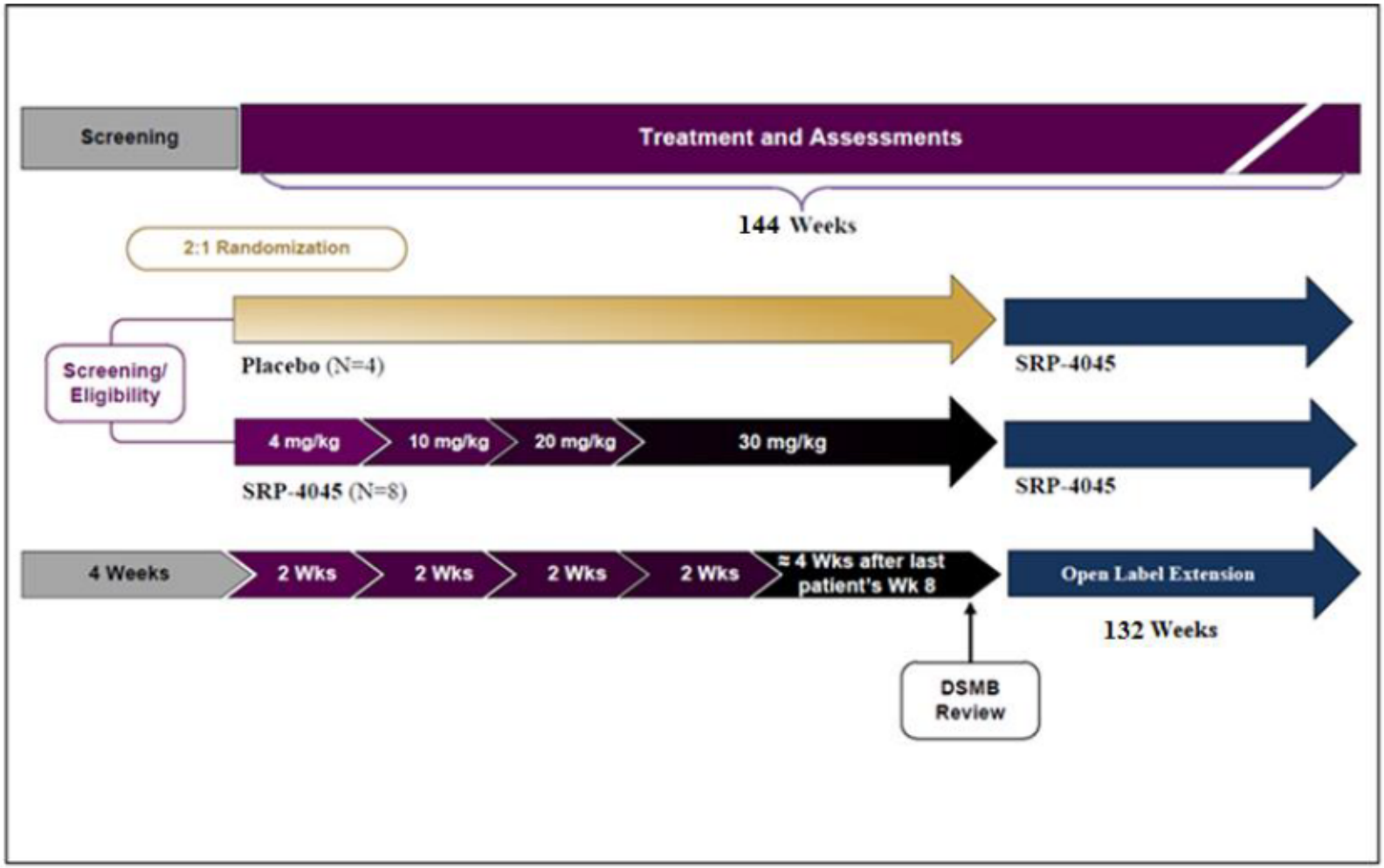
CCI [redacted] Plasma samples for serial PK determination will be collected at Baseline/Week 1 and Weeks 3, 5, 7, and 60. Urine samples for serial PK determination will be collected at Baseline/Week 1 and Weeks 3, 5, 7, and 12. CCI [redacted]

An ECG will be performed at Screening, Baseline/Week 1, Week 7, Week 12, and, then every 12 weeks. An ECHO will be performed at Screening, Week 12, and, then every 24 weeks. Clinical laboratory assessments will be performed at Screening, Baseline/Week 1, Weeks 2-9, Week 12, then, every 4 weeks to Week 36, and, then every 12 weeks. Vital signs will be assessed weekly pre- and post-infusion. Height will be assessed at Screening and, then, every 12 weeks. Weight will be assessed at Screening, Baseline/Week 1, and, then, every 4 weeks. A full physical exam will be conducted at Screening, Baseline/Week 1, Week 4, Week 12, Week 24, and, then, every 24 weeks. A brief physical exam will be conducted every 4 weeks (except at times of a full physical exam) to Week 36 and, then, every 24 weeks.

Additional safety assessments will be performed during the first 8 weeks of open-label treatment, as specified in in the Schedule of Events (Table 3).

All assessments are specified in the Schedule of Events (Table 2 and Table 3). Figure 1 is a schematic of the study design.

**Figure 1: Study Design Schematic**



## 7.2. Dose Selection Rationale

CCI

[redacted]

CCI

[redacted]

## 7.3. Study Endpoints

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

The primary endpoint is assessment of the safety of SRP-4045 during the double-blind dose-titration period according to the following:

- Incidence of AEs

[redacted]

- Incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- Incidence of abnormalities in vital signs and physical examinations
- Clinically significant worsening of ECGs and ECHO

The secondary endpoint is to determine the PK profile of SRP-4045 during the double-blind dose-titration period:

- 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 ($CL_R$)

CCI [redacted]

## 7.4. Discussion of Study Design

CCI [redacted]

[redacted]

CCI [redacted]

### 7.4.3. Choice of Endpoints

This is a Phase 1 clinical study to evaluate the safety, tolerability, and PK of SRP-4045.

CCI [redacted] were chosen for their relevance to DMD. CCI [redacted] were chosen based on the disability level expected in the study population.

[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. Males aged 7 to 21, inclusive.
2. Established clinical diagnosis of DMD with a deletion amenable to exon 45 skipping (eg, deletions of exons 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55) as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification (MLPA) or sequencing.
3. Stable cardiac and pulmonary function that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Non-ambulatory, or incapable of walking ≥300 meters on the 6-Minute Walk Test (6MWT).
5. On a stable dose of oral corticosteroids for at least 24 weeks prior to study drug administration and the dose or dose equivalent is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study, OR has not received corticosteroids for at least 24 weeks prior to study drug administration and does not expect to start corticosteroids throughout the study.
6. Patients who are post-pubertal and sexually active must agree to use, for the entire duration of the study and for 90 days post last dose, a male condom, and the female sexual partner must also use a medically acceptable form of birth control (eg, oral contraceptive).
7. Able to understand and comply with all study requirements, in the Investigator's opinion, or if under the age of 18 years, must have (a) parent(s) or legal guardian(s) who is/are able to understand and comply with all the study requirements.
8. Willing to provide informed consent to participate in the study, or if under the age of 18 years, willing to provide informed assent, if applicable, and has (a) parent(s) or legal guardian(s) who is/are willing to provide written informed consent for the patient to participate in the study.

## 8.2. 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) within 12 weeks prior to Baseline/Week 1 that might in the Investigator's judgment have an effect on muscle strength or function (eg, growth hormone, anabolic steroids). (Current growth hormone treatment for short stature will be allowed if medically indicated.)
2. Current or previous treatment with the experimental agents SMT C1100 (BMN-195) or PRO045 at any time.
3. Use of other RNA antisense or gene therapy agents.

4. Current or previous treatment with any other experimental treatment (other than deflazacort) within 12 weeks prior to Baseline/Week 1 or participation in any other interventional clinical trial within 12 weeks prior to Baseline/Week 1.
5. Use of any aminoglycoside antibiotic or statin within 12 weeks prior to Baseline/Week 1 or anticipated need for an aminoglycoside antibiotic or statin during the study.
6. Initiation or change of dosing (except for modifications to accommodate changes in weight) within 12 weeks prior to Baseline/Week 1 and/or anticipated need for a change in dosing (except for modifications to accommodate changes in weight) during the study for any of the following: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β-blockers, potassium.
7. Initiation or change of dosing within 12 weeks prior to Baseline/Week 1 and/or anticipated need for a change in dosing during the study for over-the-counter preparations such as herbal/non-herbal supplements, vitamins, minerals, and homeopathic preparations.
8. Left ventricular ejection fraction (LVEF) <40% on the Screening ECHO, and/or QTcF ≥450 msec on the Screening ECG.
9. Forced vital capacity (FVC) <50% of predicted value at Screening and/or Baseline/Week 1, and/or requirement for nocturnal ventilation.
10. Major surgery within 3 months prior to Baseline/Week 1 or planned surgery for any time during this study.
11. Presence of other clinically significant illness including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
12. Any other 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 the double-blind dose-titration period of the study will be from the time that the informed assent/consent forms are signed until approximately 4 weeks after the last patient enrolled in the study received 12 weekly doses of double-blind treatment. Based upon the findings of the DSMB in its review of dose-titration safety data, the Sponsor will determine whether to roll over patients onto open-label treatment with SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration). Treatment will continue until Study Week 144, such that the last patient enrolled will have received approximately 128 weeks of open-label SRP-4045.

After completion of treatment, patients will return for a post-treatment safety visit approximately 4 weeks after their last study infusion. The study will end once the last patient has completed his last study visit.

Follow-up for end of study is applicable for patients who complete Study 4045-101, but who do not choose to participate in the LTE study. A safety follow-up visit will occur approximately 4 weeks after the last study infusion at the end of study or for early termination. Follow-up for

early termination is required for patients who discontinue prematurely from Study 4045-101. Patients who complete Study 4045-101 per protocol and who roll over to the LTE study will not require a follow-up visit for Study 4045-101.

## 8.4. Patient Withdrawal Criteria

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

- The patient was erroneously included in the study (ie, was found to not have met the eligibility criteria specifically as it related to having a confirmed mutation amenable to exon 45 skipping.
- The patient experiences an intolerable 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. These assessments will include those listed for Week 144 and for the 4-week safety follow-up/close-out assessments (Table 2). In the case of duplicate assessments at Week 144 and the Follow-up visit, only Follow-up visit assessments should be performed. Patients who withdraw from the study will not be replaced.

# 9. TREATMENT OF PATIENTS

CCI

[redacted]

## 9.6. Administration of Investigational Drug Product

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

During the double-blind dose-titration period, eligible patients will be randomized (2:1) to receive SRP-4045 (n=8) or placebo (n=4) (Section 7.2). Patients will receive a weekly IV infusion of SRP-4045 or placebo at escalating dose levels, each for at least 2 weeks: 4 mg/kg in Weeks 1-2; 10 mg/kg in Weeks 3-4; 20 mg/kg in Weeks 5-6; and 30 mg/kg beginning on Week 7.

During the open-label extension period, all patients will receive open-label treatment with SRP-4045 30 mg/kg weekly at the study site or at home.

The dose of SRP-4045 will be calculated based on the most recent patient weight obtained at the site prior to the current visit. Infusion solutions of SRP-4045 are to be prepared by following the steps detailed in the study-specific Pharmacy Manual.

During the double-blind dose-titration period, patients, parents/caregivers, and study staff not involved with drug product preparation will be blinded to patients' treatment assignments. Throughout the study, study treatment will be administered by qualified study staff as an IV infusion over a period of approximately 35 to 60 minutes. It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream, or other topical anesthetic cream per the Investigator's discretion) be applied to the infusion site prior to each administration of study treatment. Additional administration and IP details are available in the study-specific Pharmacy Manual.

An implanted venous access port may be inserted for study treatment administration at the discretion of the Investigator. After study treatment administration and the saline flush, the port may be flushed with heparin to heplock the port prior to removal of the infusion line. If study treatment is administered into an existing IV line, the line must be flushed with normal saline before and after administration of study treatment.

No other medication may be administered concomitantly during investigational product infusions, except for heparin if infusion is via intravenous port.

All patients will be closely monitored for at least 1 hour following the completion of each infusion. If the patient does not have any infusion reactions after 48 weeks of open-label treatment, the Investigator has discretion to reduce the post-infusion observation period to 30 minutes. The following guidelines for the timing of dosing are to be followed throughout the study:

1. Patients should receive study treatment once every 7 days starting at the Baseline/Week 1 visit.
    a. After the first infusion for the duration of the double-blind placebo-controlled period, a window of ±1 day around the scheduled weekly dosing date (referenced back to the first dose at Baseline/Week 1) is acceptable.
    b. During open-label dosing, a window of ±3 days around the scheduled weekly dosing date (referenced back to the first dose at Baseline/Week 1) is acceptable.

[redacted]

2. Patients may not receive 2 separate doses of study treatment within the same 60-hour period.
3. The Medical Monitor is to be contacted in the event of a missed dose.

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

CCI

[redacted]

## 9.7. 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.

## 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. If the patient has not experienced an infusion reaction after 48 weeks of open-label treatment, the Investigator has discretion to reduce the post-infusion observation period to 30 minutes. 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 (Table 2). In addition, ECGs and ECHOs will be performed as outlined in the schedules of events.

The most likely potential drug-related AEs based on the nonclinical safety profile of SRP-4045 are expected to be related to renal function. These potential events are readily monitored through assessment of protein in the urine and by monitoring changes in serum creatinine and/or blood urea nitrogen (BUN). In addition, serum cystatin C will be used as a safety biomarker for renal clearance due to the inherently low creatinine levels in DMD patients. Kidney function will also be assessed using the urine biomarker kidney injury molecule-1 (KIM-1) (Han 2002).

CCI

[redacted]

### 9.8.2. Safety Monitoring During Dose Titration

Safety data review including AEs and laboratory assessments will be performed on an ongoing basis. The following procedures will be implemented to minimize the risk to study patients during dose titration.

- All serious adverse events (SAEs), regardless of relatedness, will be reported by the Investigators to the Sponsor immediately and no more than within 24 hours of occurrence.
- 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 occurrence.
- 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 proceed with dosing only 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. The stopping rules discussed in this section will apply only to the dose titration period of the study. If dosing of an individual patient is suspended during the open-label period, 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.

During the study, sites are required to report all AEs as defined in Section 9.8.2 and Section 10.4. If safety concerns arise at any time, dosing may be stopped until these concerns have been addressed. Dosing 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 pre-treatment values
- ≥2 patients develop 2 consecutive instances of unexplained protein in urine >2+

[redacted]

- Any unexplained gamma glutamyl transferase (GGT) >3X upper limit of normal (ULN) in combination with bilirubin >2X ULN
- 2 consecutive instances of unexplained activated partial thromboplastin time (aPTT) >45 seconds in the same patient

During the dose titration period of the study, 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. 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 employed to review all available safety data for all patients at the time point when the last patient has completed 2 infusions at 30 mg/kg (approximately Week 8). This aggregate data review will be blinded unless the DSMB specifically requests unblinding at the patient or group level based on safety data summaries. The DSMB will be charged with advising the Sponsor about whether transitioning into the open-label extension period of the protocol is appropriate based on aggregate safety data from the double-blind dose-titration period. Based on the results of the DSMB review, the Sponsor will determine whether to roll over patients into the open-label extension period.

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 the Sponsor of this study. The DSMB charter will provide 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. 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 Boards (IRB)/ Independent Ethics Committee (IEC).

## 9.9. Randomization and Blinding

### 9.9.1. Randomization

After qualifying for study entry, DMD patients with a deletion confirmed as amenable to exon 45 skipping will be randomized using a 2:1 ratio to either SRP-4045 (8 patients) or placebo (4 patients). Randomization will be performed prior to dosing at Baseline/Week 1.

### 9.9.2. Blinding for Dose Administration

This study includes a double-blind, placebo-controlled dose-titration period of at least 12 weeks during which all patients, parents, Investigators, and site staff not involved with drug product preparation will be blinded to treatment assignment. A double-blind, placebo-controlled study

design will be used to reduce potential bias during data collection and evaluation of outcome parameters.

Eight patients will receive weekly IV doses of SRP-4045, and 4 patients will receive weekly IV doses of placebo in a blinded fashion until approximately 4 weeks after the last enrolled patient received 12 weeks of treatment. Only individuals (ie, the qualified pharmacist and 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.

### 9.9.3. Unblinding Procedures

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

The reasons for any 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.

If deemed necessary, the DSMB may request to review unblinded safety data for one or more patients 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 one or more patients' data at any time.

## 9.10. Prior and Concomitant Medications and Therapeutic Procedures

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

- Oral corticosteroids for treatment of DMD including, but not limited to prednisolone and prednisone
- 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 preparations such as herbal/non-herbal supplements, vitamins, minerals, and homeopathic preparations

Other concomitant medications (excluding other RNA-antisense or gene therapy agents) 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-4045 in this study. Every attempt must be made to keep the dosage constant throughout the study period.

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

- Systemic or oral steroids for non-DMD 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 (hGH) and phosphodiesterase type 5 (PDE-5) inhibitors unless documented as medically necessary (eg, hGH prescribed by pediatric endocrinologist for treatment of short stature)
- Immunosuppressants (other than oral or systemic corticosteroids, as outlined)
- Systemic aminoglycoside antibiotics (unless discussed and agreed upon with the Investigator and the Medical Monitor)
- Statins (unless discussed and agreed upon with the Investigator and Medical Monitor)

## 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 are provided in Table 2 and Table 3.

[redacted]

## 10.1. Screening Assessments

Written informed consent and assent will be obtained from the patient and/or parent as needed, by the Investigator or delegated study staff during the Screening period. The Investigator and study staff will also review all inclusion and exclusion criteria, medical history, medication history, physiotherapeutic intervention history, and documentation of DMD diagnosis during the Screening period.

In addition, at the Screening visit, all patients will undergo additional pre-treatment tests and procedures according to the timing on the schedules of events (Table 2). These tests and procedures are listed below.

- Whole blood for genotype/single nucleotide polymorphism (SNP)
- The 6MWT (ATS 2002) will only be performed at the screening visit to determine eligibility (Table 2). 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.
- Full physical examination (Section 10.3.2)
- Vital signs (Section 10.3.1), as well as height and weight

[redacted]

- 12-lead ECG (Section 10.3.5.1)
- ECHO (Section 10.3.5.2)
- Blood and urine samples for clinical laboratory assessments (Section 10.3.3)

[redacted]

## 10.2. Baseline/Week 1 Assessments

The following Baseline/Week 1 assessments must be performed and results reviewed prior to randomization to confirm the patient is still eligible:

[redacted]

- Full physical examination (Section 10.3.2)

Once study eligibility has been confirmed at the Baseline/Week 1 visit, patients will be randomized (2:1) to blinded treatment with SRP-4045 or placebo. Patients will begin dosing at Baseline/Week 1 (Table 2).

[redacted]

Additional assessments to be performed at Baseline/Week 1 prior to dosing include:

- ECG (Section 10.3.5.1)

CCI [redacted]

- Clinical laboratory assessments

CCI [redacted]

- Pre-dose PK sample collection

Assessments to be performed at Baseline/Week 1 after dosing include:

- Plasma and urine collection for PK (Section 10.5)
- Post-infusion vital signs and observation period

Sampling for PK will be performed according to the procedures and times outlined in Section 10.5 and Table 2.

## 10.3. Safety Assessments

### 10.3.1. Vital Signs including Weight and Height

Vital signs including oral temperature, heart rate, respiratory rate and blood pressure as well as height and weight will be measured at the time points specified in the schedule of events (Table 2).

For infusion visits, vital signs are to be collected within approximately 30 minutes prior to the start of the infusion, and approximately 5, 30, and 60 minutes after the end of the infusion (ie, after investigational product has been flushed through the IV line). If the patient has not experienced an infusion reaction after 48 weeks of open-label treatment, collect vital signs prior to infusion and at 5 and 30 minutes post-infusion.

Vital signs will be performed after patients have remained seated for 5 minutes. Pulse rate and respiratory rate are to be measured over 1 minute.

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

Weight is to be reported in kilograms. If a patient's weight varies by more than 10% from the prior visit, the patient is to be re-weighed to confirm the result, and an explanation of the change must be documented.

Height is to be measured with shoes off. Ulna length should be collected measured when height is obtained for all patients. If standing height cannot be obtained, height is to be calculated using the following equation (Gauld 2004) for entry into the spirometry system:

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

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

### 10.3.2. Physical Examination

Physical examinations will be performed by the Investigator or qualified study staff prior to dose administration according the schedule of events during the dose-titration and extension study period (Table 2) and the open-label introduction study period (Table 3). The assessments in Table 3 will occur during the first 8 weeks of the open-label treatment period and are in addition to the assessments in Table 2. Duplicate assessments at the same study visit should not be performed.

A full physical examination will include review of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems. A brief physical examination will include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

### 10.3.3. Clinical Laboratory Assessments

All laboratory assessments, with the exception of PK sampling, must be performed prior to dose administration for all treatment visits.

Routine clinical laboratory testing will occur according the schedule of events during the dose-titration and extension study period (Table 2) and the open-label introduction study period (Table 3). The assessments in Table 3 will occur during the first 8 weeks of the open-label treatment period and are in addition to the assessments in Table 2. In the case of a duplicate assessment specified by Table 2 and Table 3 at the same study visit, only one assessment should be performed.

During Screening, safety laboratory assessments must be performed within 2 weeks prior to the Baseline/Week 1 visit, and results must be reviewed prior to dosing. If Screening safety laboratory samples were collected more than 2 weeks prior to the Baseline/Week 1 visit, samples must be collected again and results must be reviewed before patients may be dosed at Baseline/Week 1.

Before patients may begin dosing in the open-label extension period, safety laboratory assessments must be performed within 2 weeks prior to first dose, and the results of those labs reviewed prior to first dose. If safety laboratory samples were collected more than 2 weeks prior to the first open-label extension visit, samples must be collected again and results must be reviewed before dosing.

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 | International Normalized Ratio (INR) |
| Activated partial thromboplastin time (aPTT) | |

#### 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 | Total bilirubin |
| Cystatin C | |

#### 10.3.3.4. Urinalysis

The following parameters will be analyzed:

| | |
|---|---|
| pH | Urine microscopy |
| 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.

[redacted]

### 10.3.4. Concomitant Medications and Physiotherapeutic Intervention

Concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be reviewed and recorded at each visit (Table 2) from the time the parent(s)/guardian(s) sign(s) the informed consent and the patient signs the assent form (if applicable). Information on any physiotherapeutic intervention must be collected in detail for this study.

### 10.3.5. Other Safety Assessments

#### 10.3.5.1. Electrocardiogram (ECG)

A 12-lead ECG will be performed at the time points specified in the schedule of events for the dose-titration and extension study period (Table 2) and the open-label introduction study period (Table 3). The assessments in Table 3 will occur during the first 8 weeks of the open-label treatment period and are in addition to the assessments in Table 2. Duplicate assessments at the same study visit should not be performed.

ECGs are to be performed at a consistent time of day throughout the study. 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 pre-specified criteria. The Investigator will review the results of the centrally read ECG report and determine if abnormal findings are clinically significant.

#### 10.3.5.2. Echocardiography (ECHO)

A standard 2-dimensional (2D) ECHO will be performed at the time points specified in the schedule of events (Table 2). ECHOs will be performed at a consistent time of day throughout the study. The ECHO will be reviewed and interpreted by medically qualified personnel using a central vendor according to pre-specified criteria. Ejection fraction (EF) will be noted. The Investigator will review the results of the ECHO report and determine if abnormal findings are clinically significant.

#### 10.3.5.3. Adverse Events

The collection of AEs is described in Section 11.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

## 10.5. Pharmacokinetic Assessments

### 10.5.1. Blood Sample Collection

Blood collection for serial PK determination will occur at the time points specified in the schedule of events (Table 2): immediately pre-infusion, at approximately 5 to 10 minutes after the end of infusion, and then at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after the end of infusion at Baseline/Week 1 and Weeks 3, 5, 7, and 60.

CCI [redacted]

Blood collection for PK must be drawn from the arm contralateral to the treatment infusion. Pharmacokinetic samples may not be drawn from a patient's implanted venous port if treatment is infused via the port.

### 10.5.2. Urine Sample Collection

Urine for PK determination will be collected on a cumulative basis, during the following time intervals at the time points specified in the schedule of events (Table 2) based on start time of study drug infusion: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, and additionally at Week 7, 24-36 hours. Patients will be asked to void their bladder prior to start of study drug infusion.

# 11. ADVERSE EVENTS

## 11.1. Collection of Adverse Events

All AEs from the time of informed consent through the end of study visit (or early termination from the study) will be recorded in each individual patient's electronic case report form (eCRF). For patients who prematurely discontinue from the study (see Section 8.3), AEs will continue to be recorded until 4 weeks after the last infusion. 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.

If, at any time after the patient has completed participation in the study (see Section 8.3), the Investigator or study staff becomes 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 Screening are considered Medical History. These abnormalities will be considered AEs only if they reoccur after resolution or worsen after signing consent.

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

**Required or prolonged inpatient hospitalization:** The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations.

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

**Congenital anomaly/birth defect:** A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the 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 non-serious 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 or until the condition stabilizes or returns to baseline status or until no further follow-up is expected. The Investigator will record all information regarding the outcome of 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.

CCI [redacted]

### 11.3.8. Suspected Unexpected Serious Adverse Reactions (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) will be handled by appropriate personnel at the Sponsor or designee and reported within the required timelines in an unblinded fashion to regulatory authorities and 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 experienced from the time of informed consent/assent to the last follow-up (ie, 4 weeks after the last dose of investigational drug product) will be recorded within each patient's eCRF. 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 or study procedure or underlying disease; and any action taken will be recorded. Resolution occurs when the patient has returned to his baseline state of health or further improvement or worsening of the event is not expected.

[redacted]

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

A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE. All AEs will be followed until the resolution of AE, completion of the patient's study participation, or study termination, whichever occurs first. 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. As this is a first-in-human multicenter study, any SAE must be reported to all sites by the Sponsor or designee in an expedited fashion. Contacts for SAE reporting are provided on the SAE reporting form.

## 11.6. Special Situations

### 11.6.1. Overdose

Currently, there is no basis for determining a clinically meaningful definition of overdose for SRP-4045. 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 documented even if it does not result in an AE. An overdose will be recorded in the source documents and reported to the Sponsor or designee within 24 hours after it has been identified.

### 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 subject's treatment assignment may influence clinical decision-making, the Investigator has the option to unblind treatment assignment.

The reasons for unblinding must be noted in the source documentation. The investigator should not disclose information about treatment assignment to anyone who does not need the information due to their direct involvement in patient care.

### 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
- Determination of 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 SAE 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 AE
- 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
- Ensuring accurate recording of AEs and SAEs
- Notification of expedited SAEs 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

[redacted]

# 12. STATISTICS

## 12.1. General Considerations

This section describes the rules, conventions, statistical analysis, and presentation of data for this study, Protocol 4045-101. Full details will be provided in the final Statistical Analysis Plan (SAP) for this study.

Revisions during the study may be made to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. Any revisions will be based on blinded review of the data, as applicable. A formal SAP for the analysis and presentation of data from this study will be prepared and issued before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the clinical study report (CSR). All statistical analyses will be performed by or under 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 stated explicitly for an analysis.

Percentages of subjects with laboratory toxicities will be based on non-missing values.

Baseline will generally be defined as the last available value before dosing.

## 12.2. Determination of Sample Size

The sample size for this study is based upon qualitative considerations; no formal sample size calculations were performed. The selected sample size is considered sufficient to provide initial safety evaluation of SRP-4045 and to provide adequate data to allow for estimation of PK parameters.

## 12.3. Analysis Sets

Three analysis sets will be utilized:

**Safety Set:** All randomized patients who receive any amount of investigational drug product.

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

**Efficacy Set:** All randomized patients who have at least 1 post-baseline endpoint assessment.

## 12.4. Statistical Analysis

### 12.4.1. Protocol Deviations

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

### 12.4.2. Disposition, Demographics, and Baseline Characteristics

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

Demographic and baseline characteristics such as age (years), height (cm), weight (kg), body mass index (BMI; kg/m$^2$), CCI [redacted] will be summarized per treatment group. Demographic data and baseline characteristics 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-4045, 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.

### 12.4.6. Safety Variables

The safety and tolerability of SRP-4045 will be assessed 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. TEAEs are those AEs that develop or worsen during the on-treatment period. Non-emergent events are those that develop during the pre-treatment period
- Safety laboratory testing including hematology, coagulation, serum chemistry, and urinalysis
- Vital signs
- Physical examinations
- 12-lead ECGs
- ECHO

### 12.4.7. Safety Analyses

Safety analyses will be descriptive in nature.

Only TEAEs will be summarized. Non-emergent events will be recorded in data listings. For all AE tables, the number and percent of subjects reporting AEs (grouped by MedDRA body system and PT) will be summarized by treatment group and overall. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in frequency tables. If a subject 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:

- Treatment-emergent adverse events
- Treatment-emergent adverse events by severity
- Treatment-related treatment-emergent adverse events
- Treatment-related treatment-emergent adverse events by severity
- Treatment-emergent serious adverse events

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

The following listings will be produced:

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

Descriptive statistics for ECG, ECHO, 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.

### 12.4.8. Pharmacokinetic Analyses

The PK profile of SRP-4045 will be determined from multiple plasma samples collected serially before and after the first weekly infusion at each dose level in the dose titration phase at Weeks 1, 3, 5, and 7 and also at Week 60 in the open-label extension. In addition, multiple urine samples will be collected serially after the first infusion at each dose level in the dose titration phase and at Week 12. Individual plasma levels of SRP-4045 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-4045 will be calculated using non-compartmental 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 only for Weeks 1, 3, 5, 7, and 60 include:

- $C_{max}$
- $T_{max}$
- AUC
- $V_{ss}$

[redacted]

- $t_{½}$
- CL
- MRT
- $CL_R$

CCI [redacted] Available patient characteristics (demographics, laboratory variables, genotypes, concomitant medications, etc) will be tested as potential covariates affecting PK parameters.

CCI [redacted]

# 13. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

## 13.1. Recording of Data

Clinical data for this study will be captured in an electronic format. Electronic data capture (EDC) will be provided by a contract research organization. The Investigator, or personnel delegated by the Investigator, will perform primary data collection/perform assessments based on the protocol design and captured insource documentation. All required study information must be recorded on the appropriate CRF screens/forms using the CRF Completion Guidelines for the study. A CRF must be completed for each patient that is enrolled. 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 at regular intervals by a clinical monitor from the Sponsor or a representative of the Sponsor per the agreed upon Monitoring Plan against the source documentation for identification and clarification of any discrepancies. Automated and manual quality checks will be in place to identify discrepancies, such as missing data, protocol deviations, out-of-range data, other data inconsistencies and compliance. Requests for data clarification or correction will be documented as electronic queries within the CRF and for the Investigator or study coordinator to resolve. All changes to the CRFs will be tracked in an electronic audit trail. Site Study Files will be reviewed for compliance throughout the study.

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

The Investigator must make study files and data accessible to the study monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors such as the US Food and Drug Administration (FDA).

## 13.3. Retention of Study Documents

At study completion, all CRF data for an individual site will be copied onto a compact disc (CD) and provided to the Investigator for retention in the Study Files. The supporting Site Study Files must be retained by the Investigator for a period of 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.

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

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

If off-site archiving is used, all records should 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 should be halted or that the study center should be terminated, appropriate action may be taken after consultation among (at a minimum) the Sponsor, the Investigator, IRB/IEC and the Medical Monitor.

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

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory authorities
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements consistent with 21 CFR 312 or the European Clinical Trial Directive 2001/20/EC

Study termination and follow-up will be performed in compliance with the conditions set forth in International Council for Harmonisation (ICH) E6 on Good Clinical Practice (GCP) as well as 21 CFR 312.56b and the European Clinical Trial Directive 2001/20/EC, which require a Sponsor to ensure an Investigator's compliance with these requirements and to promptly secure a plan for compliance or discontinue shipments of the IP to the Investigator and end the Investigator's participation in the 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 US Code of Federal Regulations (CFR).

## 14.2. Regulatory and Independent Ethics Committee Review

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

The informed consent/assent documents, as prepared by the Sponsor or designee, must be reviewed and approved by the IRB/IEC and regulatory authorities, as applicable, before initiation of the study. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in the 21 CFR 50.25 and the European Clinical Trial Directive 2001/20/EC.

## 14.4. Compliance with the Protocol

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

## 14.5. Confidentiality

### 14.5.1. Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, with the exception of information that is required by law or regulations to be disclosed to the IRB/IEC, the patient's parent(s) or legal guardian(s) or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act (HIPAA) standards and/or European standards.

### 14.5.2. Patient Anonymity

The anonymity of participating patients will be maintained to the extent required by applicable laws and in accordance with current HIPAA 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 (eg, the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB/IEC, the study monitor, or the Sponsor or its representatives.

# 15. STUDY DOCUMENTATION AND GENERAL INFORMATION

## 15.1. Essential Study Documents

The following documentation will be collected prior to study enrollment:

- Signed Form FDA 1572, or equivalent
- Curriculum vitae for each person on the Form FDA 1572 or equivalent
- Signed Financial Disclosure Forms for each person listed on the Form FDA 1572 or equivalent
- IRB/IEC approval for all study materials (informed consent form [ICF], protocol, any recruitment materials, etc) and IRB/IEC membership list
- Clinical laboratory normals, when appropriate
- Clinical laboratory licenses (College of American Pathologists [CAP]/Clinical Laboratory Improvement Amendments [CLIA] or other)
- Signed final protocol page
- Investigator's Brochure acknowledgement
- A blank copy of the IRB-/IEC-approved informed consent (and assent documents, if applicable) and authorization
- A fully executed Clinical Trial Agreement and Confidentiality Agreement

Essential documentation per GCP/ICH are 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 Clinical Operations Manual and/or Regulatory Binder, must be kept on-site in a designated study site file.

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

## 15.2. General Information

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

## 15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics Inc. However, at the conclusion of this clinical study, a clinical study report will be prepared. In addition, a manuscript will be prepared for publication in a reputable scientific journal under the direction of the Sponsor. Sarepta Therapeutics Inc., will publish and

communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by Sarepta Therapeutics Inc., as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov. After completion of the study, results will be disseminated through ClinicalTrials.gov.

## 15.4. Product Handling and Complaints Reporting

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

## 16. LIST OF REFERENCES

AAOS. http://www.aaos.org/ Website accessed on: February 2014.

CCI [redacted]

Aartsma-Rus, Fokkema I, Verschuuren J, Ginjaar I, Van Deutekom J, Van Ommen GJ, 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 Resp Crit Care Med. 2002;166(1):111-7.

Beenakker EA, Fock JM, Van Tol MJ, Maurits NM, Koopman HM, Brouwer OF, 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, Alman B. 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, Mendell JR, Moxley R, Florence J, et al. Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. Neurol. 1989;39(4):475-81.

Brooke MG, Griggs RC, Mendell JR, Fenichel, GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy. I The design of the protocol. Muscle Nerve. 1981;4:186-97.

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.

CDC-MMWR. Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 Years --- four states, 2007. MMWR Morb Mortal Wkly Rep. 2009;1119-22.

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

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

CCI [redacted]

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

Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002 Jul;62(1):237-44.

[redacted]

CCI [redacted]

Kohler M, Clarenbach CF, Bahler C, Brack T, Russi EW, Bloch KE. Disability and survival in Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry. 2009;80(3):320-5.

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

CCI [redacted]

Pradhan SD, Ghosh D, Srivastava NK, Kumar A, Pandey CM, Singh U. Prednisolone in Duchenne muscular dystrophy with imminent loss of ambulation. J Neurol. 2006;253(10):1309-16.

Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults and children. Thorax. 1984;39(7):535-8.

[redacted]