

# A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy

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**Primary Objective:**The primary objective of this study is to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) compared to placebo on ambulation, endurance, and muscle function at Week 96, as measured by the 6-minute walk test (6MWT...

<b>Ethical review</b>	Not approved
<b>Status</b>	Will not start
<b>Health condition type</b>	Musculoskeletal and connective tissue disorders congenital
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON42902

### Source

ToetsingOnline

### Brief title

ESSENCE study - 4045-301

### Condition

- Musculoskeletal and connective tissue disorders congenital
- Musculoskeletal and connective tissue disorders congenital

### Synonym

Duchenne muscular dystrophy; muscle disorder

## Research involving

Human

## Sponsors and support

**Primary sponsor:** Sarepta Therapeutics, Inc.

**Source(s) of monetary or material Support:** Industry (sponsor)

## Intervention

**Keyword:** Duchenne Muscular Dystrophy, SRP-4045, SRP-4053

## Outcome measures

### Primary outcome

Primary Endpoint:

\* Change from Baseline at Week 96 on the 6MWT for the combined-active group compared to placebo.

### Secondary outcome

Secondary Endpoints:

\* Change from Baseline at Week 48 in the quantity of dystrophin protein expression as measured by Western blot of biopsied muscle tissue.

\* Change from Baseline at Week 48 in the intensity of dystrophin expression in biopsied muscle tissue, as measured by IHC.

\* Ability to rise independently from the floor (without external support) at Week 96, as indicated by an NSAA subscore of \*2\* (without modification) or \*1\* (Gower\*s maneuver).

\* LOA status at Week 96, defined as an inability to perform the 6MWT, or a result of \*0\* meters on 6MWT.

\* Change from Baseline at Week 96 in:

o NSAA total score

- o FVC% predicted
- o Frequency of falls
- o LVEF

## Study description

### Background summary

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

There are currently no disease-modifying treatments for DMD on the market. Existing interventions are largely supportive in nature and include bracing, muscle stretching exercises to avoid onset of contractures, tendon release surgery, and eventual wheelchair use and assisted ventilation.

SRP-4045 and SRP-4053 are charge neutral Phosphorodiamidate Morpholino Oligomers (PMO) that selectively binds regulatory site governing splicing of exon 45 or exon 53, respectively of dystrophin pre mRNA. In doing so, it causes the exon to be skipped during processing and restores the gene's open reading frame in patients with deletions amenable to skipping exon 45 and 53, respectively of the dystrophin gene. SRP-4045 and SRP-4053 were designed for use in patients with mutations amenable to skipping exon 45 or exon 53 each of which represent approximately 8% of all DMD patients. This is expected to enable the production of an internally truncated, yet functional, dystrophin protein, similar to that observed in Becker muscular dystrophy (BMD), a much less severe form of dystrophinopathy. In contrast to DMD, most BMD patients remain ambulatory and have a near normal life expectancy.

The main hypothesis of the study is that SRP-4045 and SRP-4053 will enable the production of a functional dystrophin protein and thus address the underlying cause for DMD in patients amenable to exon 45 and 53 skipping, respectively.

The purpose of the current study is to assess the efficacy, PK properties and safety, as well as long-term effects, safety and tolerability of SRP-4045 and

SRP-4053 in DMD patients amenable to exon 45 or 53 skipping.

## **Study objective**

### Primary Objective:

The primary objective of this study is to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) compared to placebo on ambulation, endurance, and muscle function at Week 96, as measured by the 6-minute walk test (6MWT)

### Secondary Objectives:

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

\* Dystrophin protein expression in biopsied muscle tissue as measured by:  
Western blot (quantification)

Immunohistochemistry (IHC) fiber intensity

\* Functional status as measured by:

Ability to rise independently from the floor (without external support)

Loss of ambulation (LOA)

North Star Ambulatory Assessment (NSAA)

Respiratory muscle function, as measured by forced vital capacity (FVC) % predicted

Frequency of falls

Cardiac function, as measured by left ventricular ejection fraction (LVEF)

\* Safety and tolerability of SRP-4045 and SRP-4053

### Additional Efficacy Objectives:

\* Characterize dystrophin protein expression in biopsied muscle tissue as measured by IHC (percent dystrophin-positive fibers [PDPF])

\* Evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on endurance and muscle function, as measured by:

o 10-meter walk/run time (seconds) assessed by NSAA

o Timed 4-step test

o 9-hole peg test

o Performance of the Upper Limb (PUL)

o Quantitative muscle testing (QMT) by hand-held myometry/dynamometry at all Hub Sites, and maximum voluntary isometric contraction testing (MVICT) at a subset of Hub Sites with MVICT capabilities.

\* Evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on respiratory muscle function, as measured by percent predicted maximal inspiratory pressure (MIP%p) and percent predicted maximal expiratory pressure (MEP%p).

\* Evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on patient quality of life (QoL), as measured by Pediatric Outcomes Data Collection Instrument (PODCI).

### Open-Label Treatment Period

Objectives of the open-label study period:

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

#### Pharmacokinetic Objective

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

### **Study design**

This is a double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of 2 phosphorodiamidate morpholino oligomers (PMOs), SRP-4045 and SRP-4053, in approximately 99 patients with genotypically confirmed Duchenne muscular dystrophy (DMD) with deletion mutations amenable to correction by skipping exon 45 and 53, respectively. A placebo group will be employed, and patients will be randomized in a double-blind fashion in a 2:1 ratio, combined active (SRP-4045 or SRP-4053) to placebo. A minimum enrollment target of 45 patients per genotype is planned.

### **Intervention**

If a patient qualifies for the study and agrees to take part in the clinical trial, he will undergo the procedures and assessments listed in the table below, which also specifies whether they are part of the routine monitoring for this patient population or not.

Procedure /  
Assessment  
For the purpose of this study only or routine

Full and Brief Physical  
examination  
Frequency higher than in routine  
Weight  
Frequency higher than in  
routine  
Vital  
signs  
Frequency higher than in routine  
Safety Laboratory  
Assessments  
For this study only  
DMD, LTBP4, and SPP1  
Genotyping

For this study only  
6MWT  
For this study only  
NSAA  
Frequency higher than in routine  
Time 4-step  
test  
For this study only  
9-Hole Peg  
Test  
For this study only  
QMT  
Routine  
PFT  
Frequency higher than in routine  
ECG  
For this study only  
ECHO  
Frequency higher than in routine  
Plasma for  
PK  
For this study only  
Height  
Frequency higher than in routine  
PUL  
For this study only  
Muscle  
biopsy  
For this study only  
Infusion of Study  
Drug/Placebo  
For this study only

### **Study burden and risks**

Foreseeable benefits:

No individual benefits are expected for the patients participating in this study. However, positive study results would allow for further investigations of SRP-4045 and SRP-4053. Since there are currently no disease-modifying treatments for DMD on the market, it is hoped that these investigations would ultimately provide benefit for the community of DMD patients amenable to exon 45 and 53 skipping.

Possible burden for the patient and the family related to the need to travel each week to the site for having the infusion and to have in addition the muscle biopsy.

Possible risks and adverse effects related to SRP-4045:

At this time there are no adverse events that warrant inclusion in the Development Core Safety Information (DCSI) for SRP-4045. Because the product is investigational, the DCSI is provisional. It will be reviewed, updated, and amended on an ongoing basis as further safety information becomes available. Because the kidney has been identified as the main target organ for toxicity in nonclinical studies with SRP-4045, the Sponsor has identified renal toxicity as a safety topic of interest. As such, safety monitoring for SRP-4045 includes the detection of AEs representative of renal toxicity, as well as a review of laboratory assessments related to renal function (including urine protein and creatinine). No signal for renal toxicity has been observed in the clinical setting thus far. The study is ongoing and renal function monitoring will continue throughout the course of the study.

Possible risks and adverse effects related to SRP-4053:

At this time there are no adverse events that warrant inclusion in the Development Core Safety Information (DCSI) for SRP-4053. Because the product is investigational, the DCSI is provisional. It will be reviewed, updated and amended on an ongoing basis as further safety information becomes available. Because the kidney has been identified as the main target organ for toxicity in nonclinical studies with SRP-4053, the Sponsor has identified renal toxicity as a safety topic of interest. As such, safety monitoring for SRP-4053 includes the detection of events representative of renal toxicity as well as a review of laboratory assessments related to renal function (including urine protein and creatinine). No signal for renal toxicity has been observed in the clinical setting. Renal monitoring will continue throughout the course of all studies of SRP-4053.

## Contacts

### **Public**

Sarepta Therapeutics, Inc.

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Cambridge MA 02142  
US

### **Scientific**

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215 First Street 215  
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US

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adolescents (12-15 years)

Adolescents (16-17 years)

Children (2-11 years)

### Inclusion criteria

1. Is a male with an established clinical diagnosis of DMD and an out-of-frame deletion amenable to:
  - \* Exon 45 skipping (including but not limited to deletions of exons such as 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55) OR
  - \* Exon 53 skipping (including but not limited to deletions of exons such as 42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, or 54-58) as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification or sequencing.
2. Is 7 to 13 years of age, inclusive.
3. Has stable pulmonary function (forced vital capacity % of predicted [FVC%]  $\geq$  50% and no requirement for nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Has intact right and left biceps muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Has been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: patients are allowed to take other medications (excluding other ribonucleic acid [RNA] antisense or gene therapy agents) including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs),  $\alpha$  adrenergic blockers, potassium, and coenzyme Q, provided they have been on a stable dose for 12 weeks prior to Week 1 and the dose is expected to remain constant throughout the study.
6. Achieved a mean 6MWT distance of  $\geq$  300 to  $\leq$  450 meters (without assistance) at both the Screening and Baseline visits (prior to Week 1). The mean 6MWT distance at the Screening and Baseline visits is the average of 2 separate assessments on 2 consecutive days at each visit. The Baseline mean (average of Baseline Days 1 and 2) must be within 15% of the



Screening mean distance (average of Screening Days 1 and 2).

7. Sexually active subjects must agree to use contraceptives for the entire duration of the study and for 90 days following the last dose. Both a male condom and a medically acceptable form of female contraceptive (e.g., oral contraceptives) must be used.

8. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.

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

## Exclusion criteria

1. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks prior to Week 1 that may have an effect on muscle strength or function. Growth hormone for short stature and testosterone for delayed puberty are permitted if an endocrinologist has documented the diagnosis and medical necessity of treatment, and the patient has been on a stable dose for at least 24 weeks prior to Week 1.

2. Previous treatment with SMT C1100 (BMN-195) at any time.

3. Previous treatment with PRO045 or PRO053 within 24 weeks prior to Week 1.

4. Current or previous treatment with any other experimental treatment (other than deflazacort) within 12 weeks prior to Week 1.

5. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable.

6. Presence of any other significant genetic disease other than DMD (e.g., dwarfism).

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

8. Use of any aminoglycoside antibiotic or statin within 12 weeks prior to Week 1 or anticipated need for an aminoglycoside antibiotic or statin during the study.

9. LVEF <50% on the Screening echocardiogram (ECHO) or QTcF \*450 msec based on the Screening and Baseline ECG.

10. Loss of \*30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (i.e., fixed loss of more than 10 degrees of plantar flexion from plantigrade, assuming normal range of dorsiflexion of 20 degrees).

11. Prior or ongoing medical condition that could, in the Investigator\*s opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, patients who seem unable / unwilling to comply with the study procedures, in the Investigator\*s opinion, are to be excluded.

## Study design

## Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

## Recruitment

NL	
Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

## Medical products/devices used

Product type:	Medicine
Brand name:	SRP-4045
Generic name:	N/A
Product type:	Medicine
Brand name:	SRP-4053
Generic name:	N/A

## Ethics review

Not approved	
Date:	22-11-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

## Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

<b>Register</b>	<b>ID</b>
EudraCT	EUCTR2015-002069-52-NL
ClinicalTrials.gov	NCT02500381
CCMO	NL59007.000.16