# A Phase 2, Two-Part, Multiple-Ascending-Dose Study of SRP-5051 for Dose Determination, then Dose Expansion, in Patients with Duchenne Muscular Dystrophy Amenable to Exon 51-Skipping Treatment

Published: 30-08-2019
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This study has been transitioned to CTIS with ID 2023-509935-23-00 check the CTIS register for the current data. Part A:To evaluate the safety and tolerability of multiple ascending doses of SRP-5051 (4 mg/kg, 10 mg/kg, 20 mg/kg, and 30 mg/kg),...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Musculoskeletal and connective tissue disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54626

**Source**
ToetsingOnline

**Brief title**
SRP-5051-201

### Condition

- Musculoskeletal and connective tissue disorders congenital

**Synonym**
DMD, muscular dystrophy

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Sarepta Therapeutics, Inc.
**Source(s) of monetary or material Support:** Sarepta Therapeutics;Inc.

## Intervention

**Keyword:** Duchenne Muscular Dystrophy, Exon 51, SRP-5051

## Outcome measures

### Primary outcome

Part A:

• Incidence of AEs

• Clinically significant laboratory abnormalities (eg, hematology, chemistry,

coagulation, urinalysis)

Part B:

• Change from Baseline in dystrophin protein level (as measured by Western blot

and/or other relevant methods) at 12 weeks or 24 weeks.

### Secondary outcome

Part A

PK parameters of SRP-5051 in plasma and urine, and of its major metabolite

SRP-5051A in plasma, at each dose level

Part B

• Change from Baseline in exon-skipping level (as measured by ddPCR) at 28 weeks

• Incidence of AEs

• Incidence, severity, and reversibility of hypomagnesemia

• Clinically significant laboratory abnormalities (eg, hematology, chemistry

[including electrolytes], coagulation, urinalysis)

• PK parameters of SRP-5051 in plasma and urine, and of the major metabolite

SRP-5051A in plasma

• Change from Baseline in PDPF and mean intensity, as measured by

immunofluorescence assay

# Study description

**Background summary**

Cells in our bodies contain genes, which contain instructions that tell our bodies how to grow and work by producing proteins. Genes are made up of different sections called exons. If an exon is missing, then this can prevent the production of the correct protein.

One of the proteins that our genes make is called *dystrophin.* Dystrophin is important for protecting muscles from stress and damage during activity. DMD is caused by a mutation, or change, in the gene that makes dystrophin. In some patients, DMD is caused because exon 51 is missing. If a person has DMD, his or her body is not able to make enough working dystrophin to protect his or her muscles. The study drug aims to improve dystrophin production by skipping exon 51.

**Study objective**

This study has been transitioned to CTIS with ID 2023-509935-23-00 check the CTIS register for the current data.

Part A:
To evaluate the safety and tolerability of multiple ascending doses of SRP-5051 (4 mg/kg, 10 mg/kg, 20 mg/kg, and 30 mg/kg), administered intravenously (IV) every 4 weeks, and determine the maximum tolerated dose (MTD)

Part B
To evaluate dystrophin protein level in skeletal muscle tissue following SRP-5051 treatment, administered IV every 4 weeks at the doses selected based on data from Part A

## Study design

This Phase 2, multicenter, open-label study comprises the following parts:
• Part A (multiple ascending doses [MAD]), which is intended to evaluate the safety and tolerability of SRP-5051 administered IV every 4 weeks at MAD levels, and determine the MTD

• Part B, which is intended to examine treatment with SRP-5051 administered IV every 4 weeks at the doses selected based on data from Part A, and which includes the following 2 patient cohorts:

o Previously Treated (PT) Cohort: Patients who previously received SRP-5051 treatment Part A of this study or in Study 5051-102
o Treatment-Naïve (TN) Cohort: Patients newly enrolled in the study at the beginning of Part B who have not previously received SRP-5051 treatment

## Intervention

In Part A (MAD, for dose determination), patients will receive ascending doses of SRP-5051 every 4 weeks, starting at the dose level for their assigned MAD cohort (4 mg/kg, 10 mg/kg, 20 mg/kg, or 30 mg/kg), administered by IV infusion over a period of 60 minutes (± 5 minutes).

In Part B, patients will receive SRP-5051 Q4W at one of the dose levels shown in Table 4 of the protocol. Each dose level is predicted to be in the therapeutic range, based on available dystrophin data from Part A, and to thereby warrant further evaluation (Section 7.2 of the protocol). Patients will receive their Part B study drug doses in accordance with a weight-tiered paradigm consisting of 2 body weight tiers: >= 18 kg to < 50 kg; and >= 50 kg (Table 4 of the protocol). The dose each patient receives during Part B will therefore be based on his body weight measurement at the corresponding dosing visit (refer to the Schedule of Events in Table 2 and Table 3 of the protocol).

All doses of SRP-5051 in the study are to be administered by IV infusion over a period of 60 minutes (± 5 minutes).

## Study burden and risks

Please refer to protocol tables 2 and 3 Schedule of events (pages 26-32) for more information.

During the visits, the following tests and procedures will be performed:
- Physical exam, vital signs, demographic and medical history
- ECG and echocardiogram
- Pulmonary function tests
- Questionnaires

- Blood and urine tests
- Functional tests to evaluate strength and physical ability
- Muscle biopsy

The patient participation in this study will last approximately 104 weeks. During this time the patient will visit the hospital approximately 56 times. On two occasions patients will be required to stay overnight.

Possible side effects that are already known are described in the IB and patient information letter.

The study population is required to be able to explore the feasible and reliable clinical outcome for patients at all stages of DMD, and to establish a better understanding of the progression of DMD in this population.

# Contacts

**Public**
Sarepta Therapeutics, Inc.

First Street 215
Cambridge, MA 02142
US
**Scientific**
Sarepta Therapeutics, Inc.

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US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

Elderly (65 years and older)

## Inclusion criteria

Inclusion Criteria for Patients Previously Treated with SRP-5051.
Patients previously treated with SRP-5051 must meet all of the following criteria to participate in this study:
I1. Has received prior SRP-5051 treatment in Part A of this study or in Study 5051-102.
I2. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose of study drug. The sexual partner must also use a highly effective form of contraceptive (refer to Appendix 1 of the protocol for guidance on highly effective contraceptive methods) during this timeframe.
I3. Is willing to provide informed consent or informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the patient to participate in the study.

Inclusion Criteria for Patients Treatment-Naïve to SRP-5051 Patients who are treatment-naïve to SRP-5051 must meet all of the following criteria to participate in this study:
I1. Is male.
I2. Is 7 to 21 years of age, inclusive.
I3. Has a genetic diagnosis of DMD and an out-of-frame deletion mutation of the DMD gene amenable to exon 51-skipping treatment.
I4. Has been on a stable dose of oral corticosteroids for at least 12 weeks prior to study drug administration or has not received corticosteroids for at least 12 weeks prior to study drug administration.
I 5.Has stable pulmonary function (FVC >= 40% of predicted and no requirement for nocturnal ventilation as a result of the complications of DMD) that, in the Investigator*s opinion, is unlikely to decompensate significantly over the duration of the study. NOTE: patients on nocturnal ventilation because of sleep apnea, obesity, or other conditions caused by corticosteroid use are allowed to participate in the study if FVC % predicted is >= 40
I 6. If sexually active,.
I6. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose of study drug. The sexual partner must also use a highly effective form of contraceptive (refer to Appendix 1 of the protocol for guidance on highly effective contraceptive methods) during this timeframe.
I7. Is willing to provide informed consent or informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the patient to participate in the study.

## Exclusion criteria

Exclusion Criteria for Patients Previously Treated with SRP-5051:
E 1. Has a current infection, or history of an infection within 12 weeks prior to Day -1 requiring intravenous treatment with an antibiotic, or oral antibiotics that may affect renal or cardiac function.
E 2. Has a known kidney disease (identified by eGFR [calculated using Schwartz 2012 cystatin C equation] of < 90 mL/min/1.73 m2) or had an acute kidney injury within 24 weeks prior to Screening.
E 3. Major surgery within 12 weeks prior to Screening, or planned surgery or procedures that would interfere with the conduct of the study.
E 4. Presence of other clinically significant illness, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection or malignancy.
E 5. Any other condition that, in the Investigator's opinion, could interfere with the patient's participation in the trial, including body weight loss to < 18 kg.
E 6. Inability to comply with the study protocol.
E 7. Is an employee of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator.
E 8. Any patient who is taking medications that increase the risk of bleeding, in the Investigator's opinion
E 9. Platelet count < 150 × 10^3/µL.
E 10. Known hypersensitivity to the study drug (ie, SRP-5051) or to any of its components.
E 11. Has:
a. Hypomagnesemia (< lower limit of normal) at Screening
b. Other abnormal electrolyte values considered clinically significant by the Investigator upon medical review and in consultation with the Medical Monitor at Screening;
c. Serum creatinine > upper limit of normal (ULN) at Screening.
E 12. Has quantitative urinalysis or urine microscopy findings above the ULN for RBCs or WBCs.
E 13. Urine Protein/Creatinine Ratio >= 200 mg/g and UACR >= 30 mg/g OR 24-hour urine values for protein >= 200 mg/24 hr at Screening and albumin >= 30 mg/24 hr. (Note that 24-hour urine protein does not need to be performed during screening if the UPCR/UACR criteria are met).
E 14. GGT > 3 × ULN at Screening
E 15. Is being treated with a proton pump inhibitor, loop diuretic, or thiazide diuretic at the time of study initiation.
E 16. Treatment with any exon 51-skipping therapy within 4 weeks prior to Screening, or with any experimental gene therapy for the treatment of DMD at any time.
For other exclusion criteria please refer to Protocol

Exclusion Criteria for Patients Treatment-Naïve to SRP-5051:
E 1. History of hypomagnesemia within 12 weeks prior to Screening.
For TN Cohort patients entering the study in Part B
E 2. Has body weight < 18 kg.
E 3. Has a diagnosis of diabetes (any type).
E 4. Initiation or change of dosing (except for modifications to accommodate changes in weight or changes in standard of care) within 12 weeks prior to Screening for any of the following: angiotensinconverting enzyme inhibitors, angiotensin receptor-blocking agents, β- blockers, or potassium.
E 5. Requires anti-arrhythmic and/or diuretic therapy for heart failure.
E 6. Has a current infection, or history of an infection within 12 weeks prior to Day -1 requiring intravenous treatment with an antibiotic, or oral antibiotics that may affect renal or cardiac function.
E 7.Has a known kidney disease (identified by eGFR [calculated using Schwartz cystatin C equation] of < 90 mL/min/1.73 m2) or had an acute kidney injury within 24 weeks prior to Screening.
E 8. Major surgery within 12 weeks prior to Screening, or planned surgery or procedures that would interfere with the conduct of the study.
E 9. Presence of other clinically significant illness, including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection or malignancy.
E 10. Any other condition that, in the Investigator's opinion, could interfere with the patient's participation in the trial.
E 11. Inability to comply with the study protocol.
E 12. Is an employee of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator.
E 13. Any patient who is taking medications that increase the risk of bleeding, in the Investigator's opinion
E 14. Platelet count < 150 × 10^3/µL
E 15. Known sensitivity to the study drug (ie, SRP-5051) or to any of its components
E 16. Has:
a. Hypomagnesemia (< lower limit of normal) at Screening
b. Other abnormal electrolyte values considered clinically significant by the Investigator upon medical review and in consultation with the Medical Monitor at Screening;
c. Serum creatinine > upper limit of normal (ULN) at Screening
E 17. Has quantitative urinalysis or urine microscopy findings above the ULN for RBCs or WBCs
E 18. Urine Protein/Creatinine Ratio >=200 mg/g and UACR >=30mg/g OR 24-hour urine values for protein >=200mg/24hr and albumin >= 30mg/24hr
For other exclusion criteria please refer to Protocol

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 06-07-2022 |
| Enrollment: | 6 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Registration: | No |

# Ethics review

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| Approved WMO Date: | 30-08-2019 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 24-02-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 14-04-2020 |
| Application type: | First submission |

| | |
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| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 16-07-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 01-09-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-01-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 27-12-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 24-02-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 18-11-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-01-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |

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|---|---|
| Date: | 09-06-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 25-08-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-09-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 06-11-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 08-02-2024 |
| Application type: | Amendment |
| 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

| Register | ID |
|---|---|
| EU-CTR | CTIS2023-509935-23-00 |
| EudraCT | EUCTR2019-000601-77-NL |
| ClinicalTrials.gov | NCT04004065 |
| CCMO | NL70632.000.19 |