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:Double-blind period : Evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) compared to placebo on ambulation, endurance, and muscle function, as measured by the 6MWTSecondary Objectives:- Double-blind period:...

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

Summary

ID

NL-OMON51496

Source
ToetsingOnline

Brief title
ESSENCE study - 4045-301

Condition

- Musculoskeletal and connective tissue disorders congenital
- Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)

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: Casimersen, Duchenne Muscular Dystrophy, Golodirsen

Outcome measures

Primary outcome

Double-blind period: Change from Baseline at Week 96 on the 6MWT for the

combined-active group compared to placebo.

Secondary outcome

1) *Change from Baseline at Weeks 48 or 96 in the quantity of dystrophin

protein expression as measured by Western blot of biopsied muscle

tissue

*Change from Baseline at Weeks 48 or 96 in the intensity of dystrophin

expression in biopsied muscle tissue, as measured by IHC

2) * 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)

* Time to LOA from randomization through Week 96

* Change from Baseline at Week 96 in:

- NSAA total score

- FVC% predicted

3) Review and evaluation of:

* AEs, SAEs, deaths, and discontinuations due to AEs

* Laboratory testing including hematology, coagulation, chemistry

(including serum cystatin C), electrolytes (including magnesium), and

urinalysis (including urinary kidney injury molecule-1 [KIM-1])

* Immunogenicity

* Electrocardiogram (ECG)

* Vital signs

* Physical examination findings

4) * Change from Baseline at Week 144 (Week 48 of the OL period) in 6MWT

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

at Week 144, as indicated by an NSAA subscore of "2" (without modification) or

"1" (Gower's maneuver)

* Time to LOA from randomization through Week 144

* Change from Baseline at Week 144 in:

* NSAA total score

* FVC% predicted

5) Review and evaluation of:

* AEs, SAEs, deaths, and discontinuations due to AEs

* Laboratory testing including hematology, coagulation, chemistry

(including serum cystatin C), electrolytes (including magnesium), and

urinalysis (including urinary kidney injury molecule-1 [KIM-1])

* Immunogenicity

* Electrocardiogram (ECG)

* Vital signs

* Physical examination findings

6) Standard population PK parameters will be estimated by population PK analysis. The effects of potential covariates such as standard dosing, demographic characteristics, concomitant medications, laboratory values, and others on SRP-4045 and SRP-4053 PK will be evaluated

Study description

Background summary

Duchenne muscular dystrophy (DMD) is a rare, fatal degenerative neuromuscular disease with an X-linked recessive inheritance caused by mutations in the dystrophin gene that occurs in approximately 1 in every 3500 to 5000 males worldwide. The mutations that cause DMD typically disrupt the mRNA reading frame and prevent production of dystrophin, a critically important part of the protein complex that connects the cytoskeleton of a muscle fiber to the cell membrane and extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contraction causes cellular degeneration, regeneration, and inflammation and over time, myonecrosis. The clinical effect of this disrupted dystrophin reading frame is dramatic and lethal.

The progression of DMD follows a highly predictable course. Significant motor deficits may be present during the first year of life, but diagnosis is usually made between the ages of 3 to 5 years when toddlers begin to show functional symptoms (eg, waddling gait, toe walking, and difficulty climbing stairs). Over time, ambulation becomes increasingly abnormal and by 8 years of age, most patients are losing the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking. By 10 to 14 years of age, most are wheelchair-dependent. Weakness of the arms and increasingly limited upper limb function, contractures, decubitus ulcers, and scoliosis (which often requires surgery) occur frequently.

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

Subclinical impairment of respiratory muscle function occurs in ambulatory patients, but clinical impairment of respiratory function usually only happens after loss of ambulation (LOA). Respiratory insufficiency typically starts at night, resulting in disturbed sleep, morning drowsiness and headaches, loss of appetite, and frequent pulmonary infections. Congestive heart failure or sudden death occurs in 20% of patients.
In addition to clinical manifestations, patients with DMD typically have elevated creatine kinase (CK) values due to leakage of the enzyme from degenerating muscle fibers. In DMD, CK is often 50 to 100 times normal values. High transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] up to approximately 22 × upper limit of normal [ULN]) and lactate dehydrogenase levels, originating from degenerating muscle, are also generally observed in these patients. Creatinine levels tend to be low or low normal due to decreased muscle mass, thus serum cystatin C may provide a better measure of renal function than does creatinine.

While pulmonary and cardiac functions are generally normal during early childhood, cardiac and diaphragmatic muscles progressively weaken during late childhood and adolescence, leading to eventual dependence on ventilatory support. Historically, patients typically died from respiratory or cardiac failure in their late teens or early 20s. Recent research suggests that use of ventilatory support and steroids may increase life span by several years; however, DMD still has a mortality rate of 100%. Existing interventions are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation. Current pharmacologic treatments, such as corticosteroids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function. However, their benefits are only temporary and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, cushingoid facies and habitus, and cataracts. In December 2019, golodirsen (VYONDYS 53®) received accelerated approval from the Food and Drug Administration (FDA) for the treatment of DMD in patients who have a confirmed mutation in the DMD gene that is amenable to exon 53 skipping. In February 2021, casimersen (AMONDYS 45®) received accelerated approval from the FDA for patients who suffer from DMD with mutations amenable to exon 45 skipping.

Glucocorticoids, such as deflazacort, are commonly used as treatment of DMD and have been shown to have some benefits but are associated with well-known side effects. Moreover, glucocorticoids do not address the cause of DMD (ie, the absence of dystrophin protein), which results in progressive and irreversible loss of skeletal and cardiac muscle function that eventually results in death due to cardiopulmonary decline. The clinical development program of SRP-4045 and SRP-4053 was designed to assess the efficacy and safety in patients amenable to exon 45 and exon 53 skipping respectively, receiving standard of care support measures and stable corticosteroid use.

Study objective

Primary Objective:
Double-blind period : Evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) compared to placebo on ambulation, endurance, and muscle function, as measured by the 6MWT

Secondary Objectives:
- Double-blind period: Evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on:
1) Dystrophin protein expression in biopsied muscle tissue as measured by:
* Western blot (quantification)
* Immunohistochemistry (IHC) fiber intensity
2) 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
3) Safety and tolerability of SRP-4045 and SRP-4053
- Open-label period:
4) Evaluate the long-term effects of SRP-4045 and SRP-4053 treatment on functional status up to 144 weeks
5) Evaluate the long-term safety and tolerability of SRP-4045 and SRP-4053
- Pharmacokinetics:
6) Evaluate the PK properties of SRP-4045 and SRP-4053 via a population PK model

Study design

This is a double-blind, placebo-controlled, multicenter study with an OL extension to evaluate the efficacy and safety of 2 PMOs, SRP-4045 and SRP-4053, in approximately 222 patients with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 and exon 53, respectively.
In the double-blind treatment period, a placebo group will be employed within

each genotype and patients will be randomized by genotype and age (6 to 8.5 years vs > 8.5 to 13 years) in a double-blind fashion in a 2:1 ratio, combined-active (SRP-4045 or SRP-4053) to matching placebo. Following completion of the 96-week double-blind period, all patients will begin the OL period and receive active treatment according to their genotype for up to 48 weeks. After completing the OL extension period, eligible patients may enter the LTE or Sponsor-offered program for extended treatment..

Intervention

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

Open-Label Treatment Period
Upon completion of the double-blind portion of this study, patients may participate in an OL treatment extension period of up to 48 weeks in which they will receive weekly treatment with 30 mg/kg SRP-4045 or SRP-4053, according to genotype.

Study burden and risks

Blood samples: 33 collections, 322 mL of blood in total.
Site visits: weekly, home infusion visits are also foreseen.
Physical examinations or other tests:
- blood draws: pain, light-headedness and fainting, bleeding, bruising, swelling, or infection at the puncture site
- ECG: redness, rash upon removal of sticky pads
- muscle biopsy: pain, scarring, infection, bruise, numbness near the biopsy site, or delayed wound healing.
Other potential risks described in the ICFs/Assent Forms.
Questionnaires or diaries which have to be filled in: Fall diary.
All possible discomforts that can occur during the study procedures are described in the ICFs/Assent Forms.

Contacts

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

215 First Street 215
Cambridge MA 02142
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 prior to screening by a genetic report from an accredited laboratory defining deletion endpoints by multiplex ligation-dependent probe amplification or sequencing. The patient*s amenability to exon 45 or exon 53 skipping must be confirmed prior to first dose using the genotyping results obtained during Screening.

2. Is between 6 and 13 years of age, inclusive, at randomization for patients amenable to exon 53 skipping; or is between 7 and 13 years of age, inclusive, at randomization for patients amenable to exon 45 skipping.
3. Has stable pulmonary function (FVC % of predicted *50% and no requirement for nocturnal ventilation) that, in the Investigator*s opinion, is unlikely to decompensate over the duration of the study.
4. Has intact right and left biceps brachii muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Has been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight).
6. If taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), * adrenergic blockers, aldosterone receptor antagonists, potassium, or coenzyme Q, has been on a stable dose for at least 12 weeks prior to Week 1 and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight).
7. Achieved a mean 6MWT distance of *300 to *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).
8. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose. The sexual partner must also use a medically acceptable form of contraceptive (eg, female oral contraceptives) during this time frame.
9. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.
10. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the patient to participate in the study.

Exclusion criteria

1. Treatment with any of the following investigational therapies according to the time frames specified:
* At any time:
o Utrophin upregulating agents (except for Ezutromid)
o CRISPR/Cas9, or any other form of gene editing
o Gene therapy
o Cell-based therapy (eg, stem cell transplantation)
o Any form of nucleic acid antisense therapy, except PRO045 (BMN 045) or PRO053 (BMN 053) (see below)
o Exon Skipping Therapies

- Drisapersen within 36 weeks prior to Week 1
- PRO045 (BMN 045) Within 24 weeks prior to Week 1
- PRO053 (BMN 053)Within 24 weeks prior to Week 1
- PRO051 (BMN 051) Within 24 weeks prior to Week 1
* All Anti-Myostatin Therapies within 24 Weeks prior to Week 1 including but not limited to:
o Domagrozumab (PF-06252616)
o RG-6206 (formally RO-7239361 and BMS-986089)
* Small Molecule Therapies:
o Ezutromid (SMT C1100) within 1 week prior to Week 1
* Within 24 weeks prior to Week 1:
o Anti-fibrotic or anti-inflammatory agents including but not limited to: rimeporide, epigallocatechin-gallate, TAS-205, edasalonexent (CAT-1004), FG-3019, and halofuginone (HT-100)
o Mast cell activation inhibitor (eg, CRD007 [pemirolast sodium])
o Idebenone (Raxone®)
* Within 12 weeks prior to Week 1:
o Nitric oxide (NO)-active agents including, but not limited to, metformin and citrulline, isosorbide dinitrate, tadalafil, sildenafil, pentoxifylline if taken as part of a DMD clinical trial and not for a medical indication. If taken for a medical indication, must be on a stable dose for at least 12 weeks prior to Week 1.
o Vamorolone (VBP-15)
* For any experimental treatment not otherwise specified in Exclusion Criterion 1, consult the medical monitor.
2. Treatment with any of the following non-investigational therapies according to the time frames specified:
* Within 12 weeks prior to Week 1:
o Any pharmacologic treatment (other than corticosteroids) that may have an effect on muscle strength or function. Growth hormone for short stature and testosterone for delayed puberty are permitted if a physician has documented the diagnosis and medical necessity of treatment, and the patient started dosing at least 24 weeks prior to Week 1.
* Within 12 weeks prior to Week 1 or anticipated need during the study:
o Statins
o Aminoglycoside antibiotics
3. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable.
4. Presence of any other significant genetic disease other than DMD (eg, dwarfism).
5. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
6. LVEF <50% on the Screening echocardiogram (ECHO) or QTcF *450 msec on the Screening and Baseline electrocardiogram (ECG).
7. Dorsiflexion range of motion will be measured bilaterally and recorded as degrees from neutral (see figure). The subject will be excluded if the average

loss of dorsiflexion of both extremities is > -10 degrees. For example, if the subject has -8 degrees on one side and -12 degrees on the other side, then he would still qualify because the average of the 2 sides is -10 degrees.
8. Prior or ongoing medical condition that could, in the Investigator*s opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, patients who seem unable / unwilling to comply with the study procedures, in the Investigator*s opinion, are to be excluded.
9. Known hypersensitivity to the study drug or to any of its components.

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:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Casimersen
Product type:	Medicine
Brand name:	N/A
Generic name:	Golodirsen

Ethics review

Approved WMO Date:	02-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	01-07-2022
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

Register	ID
EudraCT	EUCTR2015-002069-52-NL
ClinicalTrials.gov	NCT02500381
CCMO	NL79965.000.22