A Randomized, Double Blind, Placebo-Controlled, Study to Assess the Efficacy, Safety, and Tolerability of RO7239361 in Ambulatory Boys with Duchenne Muscular Dystrophy.

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Primary* To compare the efficacy of RO7239361 (BMS-986089) to placebo in ambulatory boys with Duchenne Muscular Dystrophy.Secondary* To compare the efficacy of RO7239361 (BMS-986089) to placebo using the following tests:- 4 stair climb velocity (…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON48814

Source
ToetsingOnline

Brief title
RO7239361

Condition

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

Synonym
Duchenne Muscular Dystrophy; Muscular Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Industrie;Sponsor

Intervention

Keyword: ambulatory boys 6 tot < 12 years, anti-myostatin agent, corticosteroids, Duchenne Muscular Dystrophy

Outcome measures

Primary outcome

The change from baseline in the North Star Ambulatory Assessment (NSAA) total

score at Week 48 in RO723936-treated participants

compared to placebo-treated participants.

Secondary outcome

* Change from baseline at Week 48 in RO7239361 treated participants compared

to placebo treated participants in the following:

- 4 stair climb velocity (4SCV)

- Stand from supine velocity

- 10 M walk/run velocity

- PODCI transfers and basic mobility subscale

- Proximal lower extremity flexor (knee extension and knee flexion)

strength, measured using manual myometry

- 6-Minute Walk Distance (6MWD)

- Clinical Global Impression of Change (CGI-C)

- Stride velocity recorded with ActiMyo

* Tabulations of the numbers of unique participants with new or worsening

laboratory abnormalities, SAEs and AEs leading to discontinuation,

in RO7239361 arms compared to the placebo arm.

Study description

Background summary

The purpose of this study is to find out if a new medicine, RO7239361 can help people with Duchenne Muscular Dystrophy (DMD). Roche also want to find out if RO7239361 is safe to take and if it is tolerated well. RO7239361 is not approved yet.
The efficacy of RO7239361 will be compared to the efficacy of a placebo. DMD is caused by a mutation in the gene that makes dystrophin. Dystrophin is important for protecting muscles from stress and damage during activity. In people with DMD, the body is not able to make enough working dystrophin to protect the muscles and the muscle mass progressively decreases. RO7239361 is an anti-myostatin agent able to block myostatin, a protein that is involved in the regulation of muscle mass. Myostatin has a negative effect on muscle growth and the muscle mass may increase by blocking myostatin.

Study objective

Primary
* To compare the efficacy of RO7239361 (BMS-986089) to placebo in ambulatory boys with Duchenne Muscular Dystrophy.

Secondary

* To compare the efficacy of RO7239361 (BMS-986089) to placebo using the following tests:
- 4 stair climb velocity (4SCV)
- Stand from supine velocity
- 10 M walk/run velocity
- PODCI transfers and basic mobility subscale
- Proximal lower extremity flexor (knee extension and knee flexion) strength, measured using manual myometry
- 6-Minute Walk Distance (6MWD)
- Clinical Global Impression of Change (CGI-C)
- Stride velocity recorded with ActiMyo

* To assess the safety and tolerability of RO7239361 in boys with DMD as reflected by new or worsening lab abnormalities (as defined by CTCAE criteria), serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation.

Tertiary/Exploratory
* To assess the safety and tolerability of RO7239361 in boys with DMD as reflected by vital signs, measures of cardiac function.
* To compare the efficacy of RO7239361 to placebo using the following tests:
- Performance of upper limb (PUL) total score
* To evaluate other measures of efficacy, quality of life and health care utilization
* To evaluate RO7239361 pharmacokinetics, pharmacodynamics, and immunogenicity
* To explore the effect of genetic variation on target engagement, pharmacodynamic (PD) effects or functional test endpoints

Study design

This is a multi-center, randomized, double-blind, placebo-controlled study.

After completion of the 48 week double blind phase, participants may enter the open label phase (up to 192 weeks) in which all participants will receive active RO7239361 study drug.

Intervention

Each participant will be administered weekly, SC doses of RO7239361 or placebo for 48 weeks in a randomized, double blind design.

1/3 - RO7239361 dose 1 (7,5 mg of 15 mg based on weight) SC weekly for 48 weeks double blind
1/3 - RO7239361 dose 2 (35 mg of 50 mg based on weight) SC weekly for 48 weeks double blind
1/3 - RO7239361 matching placebo SC weekly for 48 weeks double blind

Participants who complete the double blind phase are eligible to receive open label RO7239361 (active treatment) as part of a 192 week open-label phase of this study. Doses may be adjusted based on emerging data.

1/2 - RO7239361 dose 1 (7,5 mg of 15 mg based on weight) SC weekly for 192 weeks
1/2 - RO7239361 dose 2 (35 mg of 50 mg based on weight) SC weekly for 192 weeks

RO7239361 7.5 mg dose 10.7 mg/mL (0.7mL/syringe)
RO7239361 15 mg dose 21.4 mg/mL (0.7mL/syringe)
RO7239361 35 mg dose 50 mg/mL (0.7mL/syringe)
RO7239361 50 mg dose 71.4 mg/mL (0.7mL/syringe)

RO7239361 matching placebo 0 mg/mL (0.7mL/syringe)

Study burden and risks

In the study of healthy adults, the participants received either RO7239361 or placebo. The most frequent adverse events that occurred in the participants were injection site redness, upper respiratory tract infection, and injection site rash. All events were either mild or moderate. The people who experienced the injection site redness and rash did not have fever and the injection site redness and rash went away in most cases without treatment.
Some participants also experienced elevations in creatine kinase that did not last long. Creatine kinase can reflect muscle damage. Creatine kinase is always elevated in Duchenne patients who are able to walk.
RO7239361 has also been tested in boys with Duchenne. As of 8 February 2018, 43 boys had received doses of RO7239361. The most common adverse events (that is, occurred in more than one boy), which were considered to be related to study drug included injection site bruising, redness, irritation or rash and facial flushing. The skin events were mild to moderate, not associated with fever, and did not require that study drug be stopped. Some subjects experienced elevations in creatine kinase and liver enzymes. These elevations are usually seen in boys with Duchenne who are still able to walk and do not appear to change with RO7239361 treatment.

It is possible that an allergic reaction may occur in any individual taking a new drug.

* Subcutaneous Injection of Study drug RO7239361/ or Placebo - Local pain, bruising, bleeding, blood clot formation, a rash and in rare instances an infection might occur at the site of injection. There is also the possibility of dizziness or fainting while your child is being injected. If your child is prone to this, please inform the study personnel
* Blood Draw - Local pain, bruising, bleeding, blood clot formation, and in rare instances an infection might occur at the site of the needle stick where blood is drawn. There is also the possibility of dizziness or fainting while your child*s blood is being drawn. If your child is prone to this, please inform the study personnel.
* ECG - The ECG procedure may cause minimal discomfort during the attachment and removal of the ECG leads to and from the skin. Your child may experience some skin irritation from the electrode adhesive or develop contact dermatitis (a skin condition caused by contact between skin and some substance) that may appear as lighter or darker then the surrounding skin for possibly an extended period of time.
* ECHO - The echocardiogram procedure may cause minimal discomfort during the attachment to and removal of the electrodes from the skin.
* DXA Scan - The DXA scan may cause discomfort as your child will need to be still and may have to hold his breath for a few seconds. The amount of radiation (energy) is very small - less than one tenth the dose of a chest

x-ray, and less than a day*s exposure to natural radiation.
* Skin biopsy - If your child undergoes a skin biopsy to analyze an injection site reaction or a rash, the skin to be biopsied will be cleaned and anesthetized. Once the area is numb, a small piece of skin will be removed using a punch biopsy instrument. One or two sutures may be required to close the wound. Antibiotic ointment and a bandage will then be applied. You and your child will receive instructions for wound care. These should be followed carefully. Once the anesthetic wears off, the wound may be tender or slightly painful for a few days. After healing the area of the biopsy may have a small scar.

Contacts

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Basel 4070
CH
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* Males, * 6 to < 12 years of age at time of randomization
* Diagnosis of DMD, confirmed by medical history (eg., onset of clinical signs or symptoms before 5 years of age together with an elevated serum creatine kinase level observed before or after initial diagnosis) and by genotyping.
* Participants * 15 kg
* Ambulatory without assistance
* Participants must be receiving corticosteroids (CS, prednisone, prednisolone, or deflazacort) for at least 6 months prior to the start of study drug, with no significant change in dosage (> 0.2 mg/kg prednisone or > 0.24 mg/kg deflazacort) or dosing regimen for at least 12 weeks prior to the start of study drug, with
the expectation that dosage and dosing regimen will not change significantly for the duration of the study.
* North Star Ambulatory Assessment (NSAA) score ><=15 points at screening
* 4SC * 8 seconds at screening
* Participants must agree to avoid major changes in their physical or respiratory therapy regimen during the double blind phase, to the extent possible

Exclusion criteria

* Participants with cognitive impairment or behavioral issues that, in the judgement of the investigator, will compromise their ability to comply with study procedures.
* Participants on intermittent CS regimens with off periods of 20 days or longer (eg.: 10 days on, 20 days off).
* Any change (initiation, change in drug class, dose modification unrelated to change in body weight, interruption or re-initiation) in prophylaxis/treatment for congestive heart failure (CHF) within 12 weeks prior to start of study treatment.
* Any change (initiation, change in drug class, dose modification unrelated to change in body weight, interruption or re-initiation) in prophylaxis/treatment for bone density within 12 weeks prior to start of study treatment.
* Treatment with exon skipping therapies within 6 months prior to the start of study drug administration.
* Treatment with ataluren currently or within 12 weeks prior to the start of study drug administration.
* Concurrent or previous participation at any time in a gene therapy study.
* Participants with a FVC of < 50% of predicted value (in participants able to produce a valid FVC, as judged by the clinical evaluator or respiratory therapist)
* Cutaneous AEs sustained during participation in a prior clinical trial that resolved less than 12 weeks prior to the start of study drug administration.
* Current or prior treatment within 12 weeks prior to the start of study drug administration with androgens or human growth hormone.
* Prior treatment with RO7239361 or any other anti-myostatin agent.
* History of lower limb fracture within 12 weeks prior to the start of study drug

administration.
* History of upper limb fracture within 8 weeks prior to the start of study drug administration.
* Any injury that may impact functional testing. Previous injuries must be fully healed prior to consenting.
* Expectation of major surgical procedure, such as scoliosis surgery, during the double blind phase of this study.
* Requirement of daytime ventilator assistance
* Initiation of nighttime ventilation less than 4 weeks prior to the start of study drug administration
* Expectation that daytime or nighttime ventilation may be initiated during the double blind phase of this study.
* Clinical signs or symptoms of uncontrolled congestive heart failure (CHF) (American College of Cardiology/American Heart Associated Stage C or Stage D).
* Unwilling or unable to administer study drug at home.

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:	Recruitment stopped
Start date (anticipated):	15-08-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RO7239361

Generic name:	Anti-myostatin Adnectin

Ethics review

Approved WMO Date:	12-07-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-10-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-12-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	11-07-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	05-12-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	22-07-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2016-001654-18-NL
CCMO	NL60841.058.17