ForPatients
by Roche

Spinal Muscular Atrophy (SMA)

A clinical trial to look at how safe RO7204239 plus risdiplam is and how well this drug combination works to improve muscle function in people with spinal muscular atrophy

A Study to Investigate the Safety and Efficacy of RO7204239 in Combination With Risdiplam (RO7034067) in Participants With Spinal Muscular Atrophy

Trial Status	Trial Runs In	Trial Identifier
Active, not recruiting	12 Countries	NCT05115110 2023-506761-65-00 BN42644

The information is taken directly from public registry websites such as ClinicalTrials.gov, EuClinicalTrials.eu, ISRCTN.com, etc., and has not been edited.

Official Title:

A Two-Part, Seamless, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7204239 in Combination With Risdiplam (RO7034067) in Patients With Spinal Muscular Atrophy

Trial Summary:

Risdiplam works by helping the body produce more survival motor neuron (SMN) protein throughout the body. This means fewer motor neurons - nerve cells that pass impulses from nerves to muscles to cause movement - are lost, which may improve how well muscles work in people with SMA. RO7204239 is an investigational anti-myostatin antibody that is designed to target myostatin. Myostatin plays an important role in the regulation of skeletal muscle size by controlling growth. Inhibiting myostatin may help muscles grow in size and strength. RO7204239 in combination with risdiplam, which is designed to increase the amount of SMN protein throughout the body, has the potential to further improve motor function and clinical outcomes for people living with SMA. This trial will study the safety and efficacy of RO7204239 in combination with risdiplam in patients with spinal muscular atrophy (SMA). The trial has two parts; Part 1 is the dose-finding part in SMA patients that are either ambulant (aged 2-10 years) or non-ambulant (aged 5-10 years) within separate cohorts, and Part 2 is the pivotal part in SMA patients aged 2-25 years that are ambulant.

Hoffmann-La Roche	Phase 2/Phase 3
Sponsor	Phase

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Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	#2 Years & # 25 Years	No

1. Why is the MANATEE clinical trial needed?

Risdiplam works by helping the body produce more survival motor neuron protein throughout the body. This means fewer motor neurons (which pass impulses from the nerves to muscles, causing movement) are lost, which may improve how well muscles work in people with spinal muscular atrophy (also known as SMA). RO7204239 works by lowering the amount of myostatin protein in the body; a protein which can reduce muscle growth and development. RO7204239 with risdiplam may have a combined effect to improve muscle function in people with SMA. This clinical trial aims to compare the effects, good or bad, of RO7204239 plus risdiplam versus placebo (medicine with no active ingredients) plus risdiplam in people with SMA.

2. How does the MANATEE clinical trial work?

This clinical trial is recruiting people aged 2–25 years old with SMA. This clinical trial is split into two parts.

Part 1 will look at the safety of RO7204239 plus risdiplam and find a dose of RO7204239 that could benefit people with SMA. Part 2 will use the RO7204239 dose found during Part 1 and will study how well it works when combined with risdiplam, as well as how safe the combination is in a larger number of people with SMA. You, or your child, will only be enrolled into one part of this clinical trial.

People who take part in this clinical trial (participants) will be given a daily dose of risdiplam at the approved dose throughout the clinical trial. Participants in Part 1 who have not previously been treated with risdiplam for at least 8 continuous weeks before joining this clinical trial, and all participants in Part 2, will receive risdiplam alone for at least 8 weeks. Then, the combination treatment will be given as follows:

Part 1: RO7204239 or **placebo** every 4 weeks for 6 months. Then, participants who received placebo and risdiplam will switch treatments - everyone will be given **RO7204239** and **risdiplam** for a further 18 months.

Part 2: RO7204239 or **placebo** every 4 weeks for 18 months.

Participants may continue **RO7204239** and **risdiplam** treatment in an open-label extension phase of the clinical trial for up to 2 more years. Participants will be monitored at the clinic for at least 6 hours after the first two injections of RO7204239, and for 2 hours after the remaining injections. The clinical trial doctor will see participants regularly throughout the trial. These hospital visits will include checks to see how they respond to the treatment and any side effects they may have. Total time of participation in the clinical trial will be about 4 years, including the extension phase. Participants can stop trial treatment and leave the clinical trial at any time. After stopping treatment, participants will have follow-up appointments with the clinical trial doctor 3 months and 6 months after their last dose.

3. What are the main endpoints of the MANATEE clinical trial?

The main clinical trial endpoints (the main results measured in the trial to see if the drug has worked) are:

Part 1

The number and seriousness of any side effects

How the body processes RO7204239 and risdiplam

How RO7204239 affects the immune system and any chemical effects of RO7204239 on the body

Any change in the size of the participants' muscles

Part 2

How effective RO7204239 is, based on the participant's change in physical ability and strength

The other clinical trial endpoints for **Part 2** are:

The number and seriousness of any side effects

How the body processes RO7204239 and risdiplam

How RO7204239 affects the immune system

Any change in the size of the participants' muscles

4. Who can take part in this clinical trial?

People can take part in this trial if they:

Have SMA which has been confirmed by genetic diagnosis

Are aged 2–10 years old (Part 1) or 2–25 years old (Part 2)

Can walk/run (Parts 1 and 2) OR sit up without help, and lift a drinking cup to their mouth (Part 1 only)

People may not be able to take part in this trial if they are unable to have the required scans during the trial, or if they have taken certain other medications.

5. What experimental treatment will participants be given in this clinical trial?

Each part of the trial has two phases. The first phase is double-blinded, which means that neither the participant nor the clinical trial doctor can choose or know the group the participant is in, until the phase is over. This helps to prevent bias and expectations about what will happen. However, the participant's clinical trial doctor can find out which group the participant is in, if their safety is at risk. The double-blind phase is 'placebo-controlled', which means that one of the groups will be given a substance with no active ingredients (also known as a 'placebo'); it looks like the drug being tested but does not contain any real medicine. Comparing results from the different groups helps the researchers know whether any changes seen result from the drug or occur by chance.

In the double-blind phase of each part, everyone will be split into 2 groups randomly (like flipping a coin) and given either **RO7204239** OR a **placebo**, as an injection under the skin every 4 weeks, as well as **risdiplam**, given as a liquid to swallow at home once a day. Participants will have a 2 in 3 chance (Part 1) or a 1 in 2 chance (Part 2) of being given **RO7204239**, and a 1 in 3 chance (Part 1) or a 1 in 2 chance (Part 2) of being given **placebo**. The double-blind phase will last 6 months for participants in Part 1 and 18 months for those in Part 2.

The second phase of each part is open-label - which means everyone involved, including the participant and the clinical trial doctor, will know the clinical trial treatment the participant has been given – everyone will be given **RO7204239** plus **risdiplam** in the open-label phase.

6. Are there any risks or benefits in taking part in this clinical trial?

The safety or effectiveness of the experimental treatment or use may not be fully known at the time of the trial. Most trials involve some risks to the participant. However, it may not be greater than the risks related to routine medical care or the natural progression of the health condition. People who would like to participate will be told about any risks and benefits of taking part in the clinical trial, as well as any additional procedures, tests, or

assessments they will be asked to undergo. All of these will be described in an informed consent document (a document that provides people with the information they need to decide to volunteer for the clinical trial).

Risks associated with the clinical trial drugs

Participants may have side effects (an unwanted effect of a drug or medical treatment) from the drugs used in this clinical trial. Side effects can be mild to severe, even life-threatening, and vary from person to person. Participants will be closely monitored during the clinical trial; safety assessments will be performed regularly.

RO7204239 has not yet been tested in people with SMA. For this reason, all this drug's possible side effects may not be known now. Participants will be told about the possible side effects based on laboratory studies or knowledge of similar drugs. Participants will be told about the known side effects of **risdiplam** (given as a liquid to swallow), and possible side effects based on human and laboratory studies or knowledge of similar drugs. **RO7204239** and **placebo** will be given as an injection under the skin; participants will be told about any known side effects of injections under the skin.

Potential benefits associated with the clinical trial

Participants' health may or may not improve from participation in the clinical trial. Still, the information collected may help other people with similar medical conditions in the future.

Inclusion Criteria:

- Age at screening: Part 1 Cohorts A (ambulant participants), B (ambulant participants), and D (non-ambulant participants): 5-10 years, inclusive; Part 1 Cohort C (ambulant participants): 2-4 years, inclusive; Part 2 (ambulant participants): 2-25 years, inclusive
- Participants who have a confirmed genetic diagnosis of 5q-autosomal recessive SMA
- Symptomatic SMA disease, as per investigator's clinical judgement
- Participants who have received previous SMA disease-modifying therapies may be included provided that: Onasemnogene abeparvovec was received at least 90 days prior to screening. Participants should be tapered off steroids prior to receiving risdiplam. In addition, participants should have normal levels of liver function tests, coagulatory parameters, platelets, and troponin-I at 90 days after administration of onasemnogene abeparvovec or at least 1 month after tapering off corticosteroids, whichever comes later; Nusinersen last dose was received at least 90 days prior to screening; Risdiplam is switched to the investigational medicinal product (IMP) provided by the site

Inclusion Criteria for Part 1 Cohorts A, B, and C and Part 2 only:

- Participants who are ambulant, where ambulant is defined as able to walk/run unassisted (i.e., without the use of assistive devices such as canes, walking sticks, crutches, walkers, person/hand-held assistance, braces, orthoses, over the malleoli insoles or any other type of support) 10 meters in # 30 seconds as measures by the Timed 10-Meter Walk/Run Test [10MWRT] at screening

Inclusion Criteria for Part 1 Cohort D only:

- Participants who are able to sit, defined by: A score of 3 on Item 9 of the MFM32 (sitting without upper limb support while maintaining contact between the two hands for 5 seconds); A score of at least 2 on Item 10 of the MFM32 (while seated, leaning forward to touch a tennis ball and sitting back again, either with or without upper limb support)
- Participants who are able to raise a standardized plastic cup with a 200g weight in it to the mouth, using both hands if necessary, defined by a score of 3 on the entry item of the Revised Upper Limb Module (RULM)

Exclusion Criteria:

- Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives of the drug whichever is longer, with the exception of those who have completed a risdiplam study, or participated in a nusinersen or onasemnogene abeparvovec study
- Receiving or have received previous administration of anti-myostatin therapies
- Any history of cell therapy
- Hospitalization for a pulmonary event within the last 2 months or planned hospitalization at the time of screening
- Past surgery for scoliosis or hip fixation in the 6 months preceding screening or planned within the next 9 months (Part 1) or 21 months (Part 2)
- Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases considered to be clinically significant
- Clinically significant ECG abnormalities at screening from average of triplicate measurement, abnormal findings at echocardiography, or cardiovascular disease indicating a safety risk for participants at the time of screening
- Any major illness within 1 month before screening
- Received any multidrug and toxin extrusion (MATE1/2K) substrates within 2 weeks before screening
- Hereditary fructose intolerance
- Used any of the following medications within 90 days prior to screening: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, acetyl cholinesterase inhibitors, agents that could potentially increase or decrease muscle strength, and agents with known or presumed histone deacetylase (HDAC) inhibitory effect
- Clinically significant abnormalities in laboratory test results at the time of screening
- Ascertained or presumptive hypersensitivity to RO7204239 or risdiplam, or to the constituents of its formulations
- Clinically relevant history of anaphylactic reaction requiring inotropic support
- Any abnormal skin conditions, pigmentation or lesions in the area intended for SC injection (abdomen) and that would prevent visualization of potential injection site reactions to RO7204239
- Immobilization, surgical procedures, fracture, or trauma to the upper or lower limbs within 90 days prior to screening

Exclusion Criteria for Part 1 Cohorts A and B only:

- Participants with contraindications for MRI scan (including, but not restricted to, claustrophobia, pacemaker, artificial heart valves, cochlear implants, presence of foreign metal objects in heart or body, including spinal rods, intracranial vascular clips, insulin pumps, etc.), difficulties maintaining a prolonged supine position, or any other clinical history or examination finding that would pose a potential hazard in combination with MRI

Exclusion Criteria for Part 1 Cohort D only:

- Participants who are unable to adopt the correct position to endure adequate quality of DXA scan acquisition, as determined by the DXA scan technologist
- Participants who have contractures at screening that would interfere with DXA scan acquisition or functional assessments, as confirmed by the DXA scan technologist and clinical evaluator
- For participants able to take steps only: Able to walk unassisted (i.e., without the use of assistive devices such as canes, walking sticks, crutches, walkers, person/hand held assistance, braces, orthoses, over the malleoli insoles or any other type of support) 10 meters in # 30 seconds as measured by the timed 10MWRT at screening
- Participants who have severe scoliosis (curvature > 40°) at screening based on the participant's most recent X-ray as performed per standard of care or scoliosis that would interfere with functional assessments, as confirmed by the clinical evaluator. An X-ray is not required if it is not clinically indicated (e.g., in participants with mild scoliosis)
- Participants who require invasive ventilation, tracheostomy, or the use of noninvasive ventilation (e.g., bilevel positive airway pressure) during the daytime