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

Published: 11-01-2022
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This study has been transitioned to CTIS with ID 2023-506761-65-00 check the CTIS register for the current data. The purpose of this Phase II/III study is to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON54437

Source
ToetsingOnline

Brief title
MANATEE

Condition

- Muscle disorders

Synonym
SMA, Spinal Muscular Atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman - La Roche

Intervention

Keyword: Double Blind, Phase II/III, RO7204239 en Risdiplam, Spinal muscular atrophy (SMA)

Outcome measures

Primary outcome

part 1 (cohorts A-C):

- Evaluation of the safety of RO7204239 in combination with risdiplam compared

with placebo in combination with risdiplam

- Evaluation of PK parameters for RO7204239 when administered in combination

with risdiplam

- Evaluation of PK parameters for risdiplam when administered in combination

with RO7204239

- Evaluation of the immune response to RO7204239 in combination with risdiplam

- Evaluation of the PD effects of RO7204239 in combination with risdiplam

compared with placebo in combination with risdiplam

- Evaluation of RO7204239 PK/PD effects

Part 2:

- Evaluation of the efficacy of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam

Secondary outcome

Part 1 (cohorts A-C):

Exploratory outcome:

- Assessment of PD and efficacy of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam
- Evaluation of the efficacy of RO7204239 in combination with risdiplam by evaluation of the participant's mobility
- Evaluation of the health-related quality of life of participants treated with RO7204239 in combination with risdiplam

Part 1 (cohort D):

- Evaluation of the safety of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam
- Evaluation of PK parameters for RO7204239 when administered in combination with risdiplam
- Evaluation of PK parameters for risdiplam when administered in combination with RO7204239
- Evaluation of the immune response to RO7204239 in combination with risdiplam
- Evaluation of the PD effects of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam
- Evaluation of RO7204239 PK/PD effects

- Assessment of the efficacy of RO7204239 in combination with risdiplam

- Evaluation of the efficacy of RO7204239 in combination with risdiplam by evaluation of the participant's mobility

- Evaluation of the health-related quality of life of participants treated with RO7204239 in combination with risdiplam

Part 2:

Secondary outcome:

- Evaluation of the efficacy and PD of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam

- Evaluation of the safety of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam

- Evaluation of PK parameters for RO7204239 when administered in combination with risdiplam

- Evaluation of PK parameters for risdiplam when administered in combination with RO7204239

- Evaluation of the immune response to RO7204239 in combination with risdiplam

Exploratory outcomes:

- Evaluation of the efficacy of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam by evaluation of the participant's mobility

- Evaluation of the efficacy of RO7204239 in combination with risdiplam compared with placebo in combination with risdiplam

- Evaluation of the serum PD effects of RO7204239 in combination with risdiplam

- Evaluation of RO7204239 PK/PD/ADA effects

- Evaluation of the health related quality of life of participants treated with

RO7204239 in combination with risdiplam compared with placebo in combination

with risdiplam

Study description

Background summary

Spinal muscular atrophy is an autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and atrophy with ensuing profound motor disability commonly beginning in infancy (Crawford and Pardo 1996; Lunn and Wang 2008). In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of fingers and hands, fasciculation of the tongue, and orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections are common, particularly in SMA Type 1 (Darras 2015).

Despite the development and approval of disease modifying therapies, an unmet medical need still exists in SMA. Treated patients may not fully regain motor abilities that have been lost prior to treatment initiation. Similar findings were observed in an animal model of SMA: treated animals did not have similar outcomes to the healthy wild type control animals (Passini et al. 2010). In addition, not all patients respond in the same way to a therapeutic intervention (Talbot and Tizzano 2017).

The combination of an SMN-targeted therapy that addresses the underlying genetic driver of SMA, and a second therapeutic agent with a different mode of action targeting muscle atrophy and weakness through an alternative pathway, may lead to a complementary additive effect aiming to further improve patients* motor abilities required for daily living. One of those mechanisms is the myostatin signaling pathway, an
endogenous biological mechanism that controls skeletal muscle growth.

See also section 2.2 of the protocol

Study objective

This study has been transitioned to CTIS with ID 2023-506761-65-00 check the CTIS register for the current data.

The purpose of this Phase II/III study is to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7204239, a humanized monoclonal antibody that binds to human latent myostatin, in combination with risdiplam (Evrysdi) in patients (2-25 years of age) with spinal muscular atrophy (SMA).

Study design

This is a two-part, operationally seamless, multi-center, randomized, double-blind, placebo-controlled, Phase II/III study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7204239 in combination with risdiplam in participants (2-25 years of age) with SMA.
The study consists of two parts:
Part 1: An exploratory dose-finding part
Part 2: A confirmatory pivotal part, starting once the dose has been selected based on Part 1 data
The two parts of the study are independent, have their own objectives, and will be analyzed separately. Part 1 participants will not rollover into Part 2.

Both parts of the study require participants to be receiving risdiplam monotherapy for at least 8 continuous weeks prior to initiation of combination treatment. Thus, a run-in period is included in which only risdiplam is administered to the participants (see differences between Part 1 and Part 2 in the protocol section 4.1 and figure 1 and 2 on page 14 and 15 of the protocol). Participants will then be randomized to a combination of either RO7204239 and risdiplam or placebo and risdiplam treatment.

All participants included in both parts of the study will receive risdiplam oral solution at a dose of 5 mg once daily for participants with a body weight (BW) of 20 kg or more or 0.25 mg/kg once daily for participants with a BW of 20 kg or more throughout the study. RO7204239 will be administered every 4 weeks by SC injection into the abdomen.

N.B: As a specific requirement for The Netherlands, the Sponsor commits to the following: after the dose selection based on Part 1 data, an amended protocol containing these results and the final design of Part 2 will be submitted for the committee*s approval prior to commencing Part 2 of the study in the Netherlands.

Intervention

Part 1: Participants naïve to risdiplam will be treated with risdiplam for at least 8 weeks in the run-in period before randomization (2:1, RO7204239 plus

risdiplam: placebo plus risdiplam) into the 24 week double-blind, placebo controlled treatment period. Participants treated with risdiplam for at least 8 continuous weeks immediately prior to joining this study may be randomized to combination therapy immediately or join the run-in period and continue to receive risdiplam monotherapy until randomization, as needed to complete the number of patients required in the cohorts.

Part 2: Participants in Part 2 will complete an 8-week run-in period of treatment with risdiplam monotherapy, followed by a 72-week double-blind treatment period where patients will be randomized (1:1) to either RO7204239 plus risdiplam or placebo plus risdiplam. Participants randomized to RO7204239 will receive RO7204239 at the dose selected based on the data obtained in Part 1 of the study (the pivotal dose). Once Part 2 participants have completed the 72-week double-blind treatment period, participants will have the option to roll over into the OLE period where all participants will receive RO7204239 plus risdiplam combination treatment for an additional 2 years, unless the development of the combination therapy is stopped.

Refer also to table 6 / page 57 of the protocol

Study burden and risks

Refer to section 2.3 benefit-risk assessment of the protocol:
Taking into account the potential for patients to benefit from combination treatment with RO7204239 and risdiplam, the safety profile for both RO7204239 and risdiplam (see IB), and the risk mitigation measures for the study, the benefit/risk ratio is expected to be acceptable for this combination therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

• Confirmed genetic diagnosis of 5q-autosomal recessive SMA
• Part 2 only: available SMN2 gene copy number as previously determined by genetic testing and recorded in the participant's medical history
• Symptomatic SMA disease, as per investigator*s clinical judgement
• Age at screening:
- Part 1 Cohorts A, B, and D: 5-10 years, inclusive
- Part 1 Cohort C: 2-4 years, inclusive
- Part 2: 2-25 years, inclusive
• 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 measured by the Timed 10-Meter Walk/Run Test [10MWRT]) at screening
• 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)
• For Part 1 Cohort D only: Participants who are able to raise a standardized plastic cup with a 200 g 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).
• Participants who have received previous SMA disease-modifying therapies may be included provided that

o 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
o Nusinersen last dose was received at least 90 days prior to screening
o Risdiplam is switched to the investigational medicinal product (IMP) provided by the site
• Signed Informed Consent Form
• Signed Assent Form when appropriate and whenever possible, as determined by patient's age and individual site and country standards.
• Signed Caregiver Informed Consent Form (for part II only)
• Participants who are able and willing to comply with the study protocol and to complete all study procedures, measurements, and visits
• Negative pregnancy test at screening for females of childbearing potential
• Females of childbearing potential or who may reach childbearing potential during the study: must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception during the treatment period and for both 17 months after the final dose of RO7204239 and 28 days after the final dose of risdiplam
• For males who are expected to reach sexual maturity during the study: participants must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agree to refrain from donating sperm during the treatment period and for 28 days after the final dose of risdiplam and 4 months after the final dose of RO7204239

Exclusion criteria

• For Part 1 cohorts A and B only: Participants with contraindications for magnetic resonance imaging (MRI) scan, difficulties maintaining a prolonged supine position, or any other clinical history or examination finding that would pose a potential hazard in combination with MRI
• Part 1 Cohort D only:
- Participants who are unable to adopt the correct position to ensure 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 non-invasive ventilation (e.g., bilevel positive airway pressure) during the daytime.
• For Part 2 only: Participants who recently initiated treatment (within 6 months prior to screening) with oral salbutamol or another B2-adrenergic agonist taken orally. Participants who have been on oral salbutamol (or another B2-adrenergic agonist) for 6 months or longer before screening and have shown good tolerance are allowed. The dose of B2-adrenergic agonist should remain stable as much as possible for the duration of the study. Use of inhaled B2-adrenergic agonists (e.g., for the treatment of asthma) is allowed.
• 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. For those who have completed a risdiplam study, or participated in a nusinersen or onasemnogene abeparvovec study, the same criteria as described in Section 5.1 apply.
• Received previous administration of anti-myostatin therapies
• Any history of cell therapy
• Participants who have been hospitalized for a pulmonary event within the last 2 months or planned hospitalization at the time of screening
• Participants who have had 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)
• Participants who have unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases considered to be clinically significant
• Participants who have clinically significant electrocardiography (ECG) abnormalities at screening
• Participants with clinically significant abnormal findings at echocardiography at screening
• Participants who have had any major illness within 1 month before screening
• Participants who have received any MATE1/2K substrates within 2 weeks before screening
• Participants with hereditary fructose intolerance
• Use 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
• Participants who have clinically significant abnormalities in laboratory test results
• Participants who have ascertained or presumptive hypersensitivity to RO7204239 or risdiplam, or to the constituents of their formulations

• Participants with concomitant disease or a condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would pose an unacceptable risk to the participant in this study
•History of any malignancy (except in situ basal cell carcinoma of the skin and in situ carcinoma of the cervix of the uterus that have been excised and resolved with documented clean margins on pathology)
• Participants who have any clinically relevant history of anaphylactic reaction requiring inotropic support
• Participants who have any abnormal skin conditions, pigmentation or lesions in the area intended for subcutaneous (SC) injection (abdomen) and that would prevent visualization of potential injection site reactions to RO7204239
• Participants with immobilization, surgical procedures, fracture, or trauma to the upper or lower limbs within 90 days prior to screening
• Female participants who are pregnant or breastfeeding, or intending to become pregnant during the study or within either 17 months after the final dose of RO7204239 or 28 days after the final dose of risdiplam

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:	Recruiting
Start date (anticipated):	14-09-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Evrysdi
Generic name:	risdiplam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	RO7204239/F01-01
Generic name:	RO7204239/F01-01

Ethics review

Approved WMO Date:	11-01-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-05-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-11-2023
Application type:	Amendment
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Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-05-2024
Application type:	Amendment
Review commission:	METC NedMec

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	CTIS2023-506761-65-00
EudraCT	EUCTR2021-003417-19-NL
ClinicalTrials.gov	NCT05115110
CCMO	NL79198.041.21