ForPatients
by Roche

Spinal Muscular Atrophy (SMA)

A study to investigate the safety, tolerability, and pharmacokinetics/ pharmacodynamics of risdiplam in adult and paediatric patients with spinal muscular atrophy

Trial Status	Trial Runs In	Trial Identifier
Completed	9 Countries	NCT03032172 2016-004184-39 2023-506739-14-00 BP39054

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:

An open-label study to investigate the safety, tolerability and pharmacokinetics/pharmacodynamics of risdiplam (RO7034067) in adult and paediatric patients with spinal muscular atrophy

Trial Summary:

This is a multi-center, exploratory, non-comparative, and open-label study to investigate the safety, tolerability, PK, and PK/PD relationship of risdiplam in adults, children and infants with Spinal Muscular Atrophy (SMA) previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime or AVXS-101.

Hoffmann-La Roche	Phase 2
Sponsor	Phase

NCT03032172 2016-004184-39 2023-506739-14-00 BP39054
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	# 6 Months & # 60 Years	No

1. Why is this study needed?

Spinal muscular atrophy (SMA) is a rare genetic disorder that causes weakness and wasting (atrophy) in muscles used for movement. It is caused by loss of certain specialised

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nerve cells called motor neurons that transmit signals from the brain to the muscles, enabling movement. The cause of SMA is a structural change in a section of a gene called survival of motor neuron (SMN). The normal SMN gene provides instructions for SMN protein production. In people with SMA, due to a lack of normal SMN protein, the function of the special nerve cells that enable movement is affected.

This study is testing a medicine called risdiplam (RO7034067), which is the first drug to be given by mouth for treatment of SMA. Risdiplam is approved for use in patients with SMA, however, it is considered an experimental drug for the purpose of this study.

This study aims to find out the safety of risdiplam, how well the body handles it, and to understand how risdiplam gets to different parts of the body, how the body changes and gets rid of it in people living with SMA who have received other medicines for SMA.

2. Who can take part in the study?

People living with SMA between 6 months to 60 years of age are taking part in this study. People who previously took part in study BP39420 (Moonfish) or were previously treated with other SMA medicines called nusinersen (SPINRAZA), AVXS-101 (ZOLGENSMA) or olesoxime only could participate in this study.

People having any other major existing condition or who received any protocol-specified medicines previously, were not able to take part in this study.

People who were pregnant, or breastfeeding could not participate in the study.

3. How does this study work?

People with SMA were screened to check if they could participate in the study. The screening took place for about 28 days before the start of treatment.

Everyone who joined this study is given a daily oral dose of risdiplam as a liquid medicine. The doses of risdiplam depend on the participant’s body weight. Participants initially received risdiplam for 2 years. After completion of 2 years, they were given an opportunity to continue receiving risdiplam in the extension phase of this study for the next 3 years. Participants have regular blood tests and are checked for unwanted effects throughout the study.

This is an open-label study. This means everyone involved, including the participant and the study doctor, will know the study treatment the participant has been given.

During this study, the study doctor met the participants four times during the first month and then every 3 months thereafter. They will see how well the treatment is working and any unwanted effects participants may have. Participants will have a follow-up

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telephone call from the study doctor to check on their well-being at 30 days of completing the study treatment. This follow-up call will be conducted only for participants who stop risdiplam treatment. Total time of participation in the study will be approximately 5 years. Participants have the right to stop study treatment and leave the study at any time, if they wish to do so.

4. What are the main results measured in this study?

The main results measured in the study to assess if the medicine has worked as expected are:

- The number of participants with unwanted effects and the severity of the unwanted effects which will be assessed from the start of study treatment up to 5 years.
- How well the body processes risdiplam, which was assessed for up to 2 years.

The study additionally collected information about changes in the levels of SMN protein in blood which was measured from the start of the study up to 2 years.

5. Are there any risks or benefits in taking part in this study?

Taking part in the study may or may not make participants feel better. But the information collected in the study can help other people with similar health conditions in the future.

The study involves some risks to the participant. But these risks are generally not greater than those related to routine medical care or the natural progression of SMA. People interested in taking part were informed about the risks and benefits, as well as any additional procedures or tests they may need to undergo. All details of the study were described in an informed consent document. This included information about possible effects and other options of treatment.

Risks associated with risdiplam

Participants may have unwanted effects of the drug used in this study. These unwanted effects can be mild to severe and vary from person to person. During this study, participants will have regular check-ups to see if there are any unwanted effects.

Participants were told about the known unwanted effects of risdiplam, and possible unwanted effects based on human and laboratory studies or knowledge of similar medicines. Known unwanted effects include cold, runny nose, headache, frequent watery stools (diarrhoea), vomiting and rash.

Risdiplam is given as a liquid medicine to be taken by mouth.

The study medicine may be harmful to an unborn baby. Women and men must take precautions to avoid exposing an unborn baby to the study treatment.

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Inclusion Criteria:

- Confirmed diagnosis of 5q-autosomal recessive SMA
- Previous enrollment in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previous treatment with any of the following: 1.) Nusinersen (defined as having received >= 4 doses of nusinersen, provided that the last dose was received >= 90 days prior to screening) or 2.) Olesoxime (provided that the last dose was received <= 12 months and >= 90 days prior to screening) or 3.) AVXS-101 (provided that the time of treatment was >= 12 months prior to screening)
- Adequately recovered from any acute illness at the time of screening and considered well enough to participate in the opinion of the Investigator
- For women of childbearing potential: negative blood pregnancy test at screening, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs for at least 28 days after the final dose of study drug
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm
- For participants aged 2 years or younger at screening: 1.) Parent or caregiver of participant is willing to consider nasogastric, naso-jejunal or gastrostomy tube placement, as recommended by the Investigator, during the study to maintain safe hydration, nutrition and treatment delivery; 2.) Parent or caregiver of participant is willing to consider the use of non-invasive ventilation, as recommended by the Investigator during the study

Exclusion Criteria:

- Inability to meet study requirements
- Concomitant participation in any investigational drug or device study
- 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 studies of olesoxime, AVXS-101, or nusinersen
- Any history of gene or cell therapy, with the exception of AVXS-101
- Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator
- Inadequate venous or capillary blood access for the study procedures, in the opinion of the Investigator
- For patients aged < 2 years, hospitalization for a pulmonary event within 2 months prior to screening and pulmonary function not fully recovered at the time of screening
- Lactating women
- Suspicion of regular consumption of drugs of abuse
- For adults and adolescents only, positive urine test for drugs of abuse or alcohol at screening or Day -1 visit
- Presence of clinically significant electrocardiogram (ECG) abnormalities before study drug administration from average of triplicate measurement or cardiovascular disease
- History of malignancy if not considered cured
- For participants aged > 6 years, significant risk for suicidal behavior, in the opinion of the Investigator as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration
- Recently initiated treatment for spinal muscular atrophy (within <6 weeks prior to enrollment) with oral salbutamol or another beta 2-adrenergic agonist taken orally
- Any prior use of chloroquine, hydroxychloroquine, retigabin, vigabatrin or thioridazine, is not allowed
- Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation

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- Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study
- Recent history (less than one year) of ophthalmological diseases
- Any prior use of an inhibitor or inducer of FMO1 or FMO3 taken within 2 weeks (or within 5 elimination half-lives, whichever is longer) prior to dosing

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