# Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK 015 in Patients with Later onset Spinal Muscular Atrophy (TOPAZ)

Published: 03-04-2019 Last updated: 10-01-2025

Objectives for both the Treatment Period and Extension Period:Primary Objectives: - To assess safety and tolerability of the study medicine in patients with later onset (e.g., Type 2 and Type 3) spinal muscular atrophy (SMA)- To assess the efficacy...

**Ethical review** Approved WMO **Status** Completed

**Health condition type** Musculoskeletal and connective tissue disorders congenital

**Study type** Interventional

# **Summary**

### ID

NL-OMON55820

### **Source**

ToetsingOnline

**Brief title** 

**TOPAZ Study** 

### **Condition**

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

### **Synonym**

(Later-Onset) Spinal Muscular Atrophy, neurological muscle disease

### Research involving

Human

**Sponsors and support Primary sponsor:** Scholar Rock Inc. **Source(s) of monetary or material Support:** Scholar Rock;Inc. Intervention **Keyword:** Muscle disease, SMA Type 2 and 3, Spinal Muscular Atrophy **Outcome measures Primary outcome** Efficacy: Cohort 1 (Ambulatory Type 3 Patients): **Primary Efficacy Endpoint:** - Change from Baseline in the RHS total score at Day 364 (Visit 15) Cohort 2 (Type 2 and nonambulatory Type 3 patients) and Cohort 3 (Type 2 patients): Primary Efficacy Endpoint: - Change from Baseline in HFMSE total score at Day 364 (Visit 15) Safety: Safety will be evaluated based on occurrence of or changes in the following parameters:

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- Treatment-emergent adverse events (TEAEs) and SAEs

- Vital signs, including blood pressure, heart rate, body temperature, and respiratory rate
- Height and weight
- Physical examinations
- Laboratory assessments (hematology, serum chemistry, coagulation, urinalysis)
- 12 lead electrocardiogram (ECG)
- Concomitant medications Safety assessments may be revised if any important safety signals emerge from any ongoing clinical studies (including this study).

### **Secondary outcome**

Cohort 1 (Ambulatory Type 3 Patients)

### Secondary Efficacy Endpoints:

- Change from Baseline in the RHS total score at other prespecified timepoints
- Proportion of patients achieving various magnitudes of change in RHS score from Baseline
- Change from Baseline in 6 Minute Walk Test (6MWT)
- Change from Baseline in 30 Second sit to stand
- Change from Baseline in 10 Meter Walk/Run (from the RHS)
- Change from Baseline in timed rise from floor (from the RHS)

### Tertiary Endpoints:

- Change from Baseline in Pediatric Evaluation of Disability Inventory Computer
  Adaptive Test (PEDI CAT)
- Change from Baseline in Patient-reported Outcomes Measurement Information
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System (PROMIS) Fatigue Questionnaire

Cohort 2 (Type 2 and nonambulatory Type 3 Patients) and Cohort 3 (Type 2 Patients) :

### Secondary Efficacy Endpoints:

- Change from Baseline in HFMSE total score at other prespecified timepoints
- Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline
- Change from Baseline in Revised Upper Limb Module (RULM) total score
- Change from Baseline in number of WHO motor development milestones attained
- Proportion of patients achieving various magnitudes of change in RULM score from Baseline
- Proportion of patients who attain a new WHO motor development milestone relative to Baseline

### **Tertiary Endpoints:**

- Change from Baseline in Time to limitation on Endurance Shuttle Nine Hole Peg
  Test (ESNHPT) or Endurance Shuttle Box and Block Test (ESBBT)
- Change from Baseline in PEDI-CAT
- Change from Baseline in PROMIS Fatigue Questionnaire

### Additional Tertiary Endpoint for Cohort 3:

- Time to therapeutic effect (described in the Statistical Analysis Plan [SAP])
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# **Study description**

### **Background summary**

Later-Onset Spinal Muscular Atrophy (SMA) is an inherited disease of the motor nerves (the nerves that send signals from your brain to the muscles) causing muscle weakness. The study medicine is being developed towards the goal of treating diseases of muscle atrophy. Muscle atrophy is a condition in which muscles are smaller and weaker than normal, such as in SMA. There are currently no approved muscle-directed therapies for the treatment of SMA.

The study medicine is a protein that acts upon a muscle protein called myostatin. Myostatin is one of the factors that control the size and function of muscles. Results from animal research studies show that the study medicine may block myostatin and might cause muscles to grow larger and larger. The study medicine increased muscle size in healthy mice, rats, and monkeys. In two animal experiments of mice with SMA, treatment with the study medicine led to increases in muscle size and strength. These results show that the study medicine might have potential in treating diseases of muscle atrophy like SMA in humans.

SRK-015 has not been administrated to children prior to this research study. It has also not been administrated to any children or adults with SMA prior to this study.

### Study objective

Objectives for both the Treatment Period and Extension Period:

### Primary Objectives:

- To assess safety and tolerability of the study medicine in patients with later onset (e.g., Type 2 and Type 3) spinal muscular atrophy (SMA)
- To assess the efficacy of the study medicine by assessing changes in motor function outcome measures in 3 separate predefined cohorts

### Secondary Objectives:

- To characterize the pharmacokinetics (PK) of the study medicine
- To evaluate the pharmacodynamic (PD) effects of the study medicine
- To evaluate time to the rapeutic effect between low and high dose of the study medicine in a predefined cohort (Cohort 3)
- To evaluate the immunogenicity of the study medicine

- To evaluate the effect of the study medicine on quality of life

### Study design

This study will be conducted in approximately 20 study sites across the United States and Europe to evaluate the safety and efficacy of the study medicine in later-onset SMA patients (e.g., patients with Type 2 and Type 3 SMA) age 2 through 21 years old. Patients may receive the study medicine on top of an approved SMA treatment or may receive it as monotherapy. Approximately 55 male and female patients with later onset SMA will be enrolled across 3 separate parallel subpopulations subsequently described as cohorts. Patients will receive the study medicine every 4 weeks during the 52-week Treatment Period, with patients in Cohorts 1 and 2 directly assigned high dose (20 mg/kg) of the study medicine and patients in Cohort 3 randomized 1:1 double blind between low dose (2 mg/kg) and high dose (20 mg/kg) of the study medicine.

### Intervention

### Treatment Period:

High dose of the study medicine will be 20 mg/kg and low dose will be 2 mg/kg. Doses will be diluted in normal saline and administered via IV over 2 hours + 10-minute window. If there are no acute reactions following the first two doses for a patient, and if the Investigator determines that it would be safe to do so, the infusion duration can be changed to less than two hours but no shorter than 1 hour. Total study participation for an individual patient will consist of approximately 4 weeks for Screening, 52 weeks of study visits, if the patient does not enroll into the Extension Period A, 12 weeks Safety Follow-up for a total duration of approximately 68 weeks (approximately 16 months).

### Extension Period A:

Patient will receive the study medicine by IV infusion in the same manner in which he/she received the study medicine during his/her participation in the Treatment Period. Total study participation for an individual patient who completes both Treatment and Extension Period A will consist of approximately 4 weeks for Screening, 104 weeks of study visits, and 12 weeks Safety Follow-up for a total duration of approximately 120 weeks (approximately 28 months).

### Extension Period B:

Patient will receive the study medicine by IV infusion in the same manner in which he/she received the study medicine during his/her participation in the Extension Period A. Total study participation for an individual patient who completes the Treatment Period and Extension Periods A and B will consist of approximately 4 weeks for Screening, 156 weeks of study visits, and 12 weeks of

Safety Follow-up for a total duration of approximately 172 weeks (approximately 40 months).

### Extension Period C:

Patient will receive the study medicine by IV infusion in the same manner in which he/she received the study medicine during his/her participation in the Extension Period B. Total study participation for an individual patient who completes the Treatment Period and Extension Periods A, B, and C will consist of approximately 4 weeks for Screening, 208 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 224 weeks (approximately 52 months).

### Study burden and risks

Participation of this study (without enrollment in the Extenstion Period A, B and C) will comprise approximately 16 months. The total duration of study participation including all Extension Periods (A, B and C) will be approximately 52 months. During this study the following procedures will be performed: Physical exam, vital signs check (including heart rate, blood pressure, temperature and breathing rate), ECG, several motor function tests, completion of questionnaires, blood and urine tests (incl. pregnancy test if applicable), and treatment with the study medicine.

Consequences of these procedures could include: When taking blood samples the subject may feel pain or be light-headed. Additional bleeding, temporary discomfort, bruising, and infections (rare) could occur when drawing blood. During an ECG subjects may experience temporary discomfort (e.g. pulling hair/skin during the removal of sensors), subjects might develop minor skin irritation from the ECG patch adhesive. Concerning the examination of motor functions there is a risk that subjects could fall down/over when attempting to complete exercises. Regarding the study medicine, 58 healthy individuals have received the study medicine in a previous clinical trial. The most common adverse effects observed in this research study were headache (26%), pyrexia (fever, 24%), sinus infection (22%), nasopharyngitis (common cold, 22%), cough (22%), vomiting (16%), rash (16%), nausea (14%), fall (14%), scoliosis (12%), nasal congestion (10%) and dizziness (10%). The majority of these adverse events were considered mild or moderate in severity.

# **Contacts**

### **Public**

Scholar Rock Inc.

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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

- 1. Age 5 through 21 years old at the time of screening for Cohorts 1 and 2; Age 2 years old at the time of screening for Cohort 3
- 2. Estimated life expectancy >2 years from screening
- 3. Informed consent document signed by the patient if the patient is legally an adult. If the patient is legally a minor, informed consent document signed by the patients parent or legal guardian and patients oral or written assent obtained, if applicable and in accordance with the regulatory and legal requirements of the participating location
- 4. Documented diagnosis of 5q SMA
- 5. Diagnosed as later onset (e.g., Type 2 or Type 3) SMA prior to receiving any treatment with therapy approved for SMA
- 6. Non ambulatory patients must be able to sit independently (sits up straight
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with head erect for at least 10 seconds; does not use arms or hands to balance body or support position) per World Health Organization (WHO) motor milestones definition at screening. Patients who never had the ability to walk independently will be classified as Type 2. Patients who previously had the ability to walk unaided will be classified as Type 3.

- 7. Ambulatory patients must have the ability to independently ambulate without aids or orthotics over 10 meters at screening
- 8. For Cohort 1, Revised Hammersmith Scale (RHS) score no greater than 63 at screening
- 9. For Cohorts 2 and 3, Hammersmith Functional Motor Scale Expanded (HFMSE) score no less than 10 at screening
- 10. Receiving the same background SMA therapy (e.g., on an approved survival motor neuron (SMN) upregulator therapy such as nusinersen, or not on any SMA therapy) for at least 6 months prior to screening and anticipated to remain on that therapy throughout the duration of the study a. If receiving the SMN upregulator therapy nusinersen, must have completed the loading regimen and initiated maintenance dosing (i.e., completed at least one maintenance dose) with at least 4 weeks after the first maintenance dose having elapsed prior to screening
- 11. Nutritional status stable over the past 6 months and anticipated to be stable throughout the duration of the study
- 12. Have no physical limitations that would prevent the patient from undergoing motor function outcome measures throughout the duration of the study
- 13. Able to receive study drug infusions and provide blood samples through the use of a peripheral intravenous (IV) or a long-term IV access device that the patient has placed for reasons independent from the study (i.e., for background medical care and not for the purpose of receiving SRK-015 in the study), throughout the duration of the study
- 14. Able to adhere to the requirements of the protocol, including travel to the study center and completing all study procedures and study visits
- 15. For patients who are expected to have reached reproductive maturity by the end of the study, adhere to study specific contraception requirements
- a. Females of childbearing potential (see Section 10.1.7.4 for definition) must have a negative pregnancy test at screening and agree to employ highly effective contraceptive measures (failure rate of 1% or less per year when used consistently and correctly) for the duration of the study and for 18 weeks following the last
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dose of study drug. Effective contraception methods are restricted to combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral,

intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine

hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. In the context of this guidance, sexual abstinence is considered a highly effective

method only if defined as refraining from hetrosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be

evaluated in relation to the duration of the clincial trial and the preferred and lifestyle of the patient.

b. Male patients with female partners of childbearing potential must be abstinent or agree to employ the use of a condom with or without spermicide throughout the duration of the study and for 18 weeks following the last dose of study drug.

### **Exclusion criteria**

- 1. Use of tracheostomy with positive pressure
- 2. Use of chronic daytime non invasive ventilatory support for >16 hours daily in the 2 weeks prior to dosing, or anticipated to regularly receive such daytime ventilator support chronically over the duration of the study
- 3. Any acute or comorbid condition interfering with the well being of the patient within 14 days of screening, including active systemic infection, the need for acute treatment or inpatient observation due to any reason
- 4. Severe scoliosis and/or contractures at screening. Based on clinical judgment, any scoliosis or contractures present must be stable over the past 6 months, anticipated to be stable for the duration of the study and not prevent the patient from being evaluated on any functional outcome measures throughout the duration of the study.
- 5. Pregnant or breastfeeding
- 6. Major orthopedic or other interventional procedure, including spine or hip surgery, considered to have the potential to substantially limit the ability of the patient to be evaluated on any functional outcome measures, within 6 months prior to screening, or anticipated for the duration of the study

- 7. Prior history of a hypersensitivity reaction to a monoclonal antibody (mAb) or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein), SRK-015, or excipients of SRK-015
- 8. Use of systemic corticosteroids within 60 days prior to screening. Inhaled or topical steroids are allowed.
- 9. Treatment with investigational drugs within 3 months or 5 half-lives, whichever is longer prior to screening
- 10. Use of therapies with potentially significant muscle effects (such as androgens, insulin-like growth factor, growth hormone, systemic beta-agonist, botulinum toxin, or muscle relaxants or muscle-enhancing supplements) or potentially significant neuromuscular effects (such as acetylcholinesterase inhibitors) other than approved SMN upregulator therapy within 60 days prior to screening.
- 11. Use of valproic acid within 60 days prior to screening.
- 12. Patient has any other condition, which in the opinion of the Investigator may compromise safety or compliance, would preclude the patient from successful completion of the study, or interfere with the interpretation of the results.

# Study design

# **Design**

Study phase: 2

Study type: Interventional

Intervention model: Parallel

Allocation: Randomized controlled trial

Masking: Double blinded (masking used)

Control: Active

Primary purpose: Treatment

### Recruitment

NL

Recruitment status: Completed
Start date (anticipated): 14-11-2019

Enrollment: 2

Type: Actual

# Medical products/devices used

Product type: Medicine
Brand name: SRK-015

Generic name: human anti-proMyostatin monoclonal antibody

# **Ethics review**

Approved WMO

Date: 03-04-2019

Application type: First submission

Review commission: METC NedMec

Approved WMO

Date: 30-10-2019

Application type: First submission

Review commission: METC NedMec

Approved WMO

Date: 12-12-2019

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 20-12-2019

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 11-03-2020

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 12-03-2020

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 09-09-2020

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 11-09-2020

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 16-03-2021

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 18-03-2021

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 09-05-2021

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 14-05-2021

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 10-10-2021

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 27-10-2021

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 28-01-2022

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 21-02-2022

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 16-08-2022

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 31-08-2022

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 01-05-2023

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 11-05-2023

Application type: Amendment

Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date: 02-06-2023

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 15-06-2023

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 23-11-2023

Application type: Amendment

Review commission: METC NedMec

Approved WMO

Date: 20-12-2023

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

EudraCT EUCTR2018-004383-65-NL

ClinicalTrials.gov NCT03921528 CCMO NL69360.041.19

# **Study results**

Date completed: 16-01-2024 Results posted: 18-10-2024

**First publication** 

03-10-2024