Phase 3, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Apitegromab (SRK-015) in Patients with Later-Onset Spinal Muscular Atrophy Receiving Background Nusinersen or Risdiplam Therapy

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Primary-Assess the efficacy of apitegromab compared with placebo using the HFMSE in patients 2 through 12 years oldKey secondary-Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON51312

Source
ToetsingOnline

Brief title
SRK-015-003

Condition

- Neuromuscular disorders

Synonym
neuromuscular disease, SMA

Research involving

Human

Sponsors and support

Primary sponsor: Scholar Rock Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Phase 3, Spinal Muscular Atrophy

Outcome measures

Primary outcome

Change from Baseline in HFMSE total score at 12 months

Secondary outcome

-Proportion of patients with >=3-point change from Baseline in the HFMSE total

score at 12 months

-Change from Baseline in RULM total score at 12 months

-Change from Baseline in number of WHO motor development milestones attained at

12 months

Study description

Background summary

SMA is a whole-body disease (Wirth 2020). Although the SMN-targeted therapies, which include gene therapy (onasemnogene abeparvovec-xioi [ZOLGENSMA®]) and the SMN upregulator (also referred to as SMN corrector) therapies nusinersen and risdiplam, approved for the treatment of SMA have been shown to significantly improve clinical outcomes by preventing or reducing the decline in motor function, patients may continue to suffer from substantial motor functional impairment because SMN-targeted therapies focus on SMN-dependent pathways and do not directly impact skeletal muscle to reverse the atrophy that has already taken place (Mercuri 2018, Mercuri 2020).
Consequently, there remains an unmet medical need for a complementary therapeutic strategy, namely muscle-directed therapy, that may address muscle

atrophy and thereby improve motor function in patients with SMA. Through its novel mechanism of action as a selective inhibitor of myostatin activation, apitegromab (SRK-015) has the potential to produce a clinically meaningful effect on motor function in a broad population of patients with SMA who are being treated with background SMN upregulator therapies (e.g., nusinersen [SPINRAZA®] or risdiplam [EVRYSDI®]) (SPINRAZA Food and Drug Administration [FDA] Prescribing Information [PI] 2020, SPINRAZA Summary of Product Characteristics [SmPC] 2022, EVRYSDI FDA PI 2022, EVRYSDI SmPC 2022).

Study objective

Primary
-Assess the efficacy of apitegromab compared with placebo using the HFMSE in patients 2 through 12 years old

Key secondary
-Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement in patients 2 through 12 years old
-Assess the efficacy of apitegromab compared with placebo by measuring changes in upper limb function using the Revised Upper Limb Module (RULM) in patients 2 through 12 years old
-Assess the efficacy of apitegromab compared with placebo by measuring changes in number of World Health Organization (WHO) motor development milestones in patients 2 through 12 years old

Study design

This Phase 3 trial will be conducted at approximately 55 to 60 trial sites globally to evaluate the safety and efficacy of apitegromab compared with placebo as an adjunctive therapy to nusinersen or risdiplam in nonambulatory patients with later-onset SMA. In the Main Efficacy Population, 2 dose levels of apitegromab will be evaluated to further assess the lowest efficacious dose level. Patients will be randomized to receive apitegromab (10 mg/kg or 20 mg/kg) or matching placebo by intravenous (IV) infusion. The trial will include Screening, Treatment, and Safety Follow-up Periods.

Intervention

• For the Main Efficacy Population, approximately 156 patients who are 2 through 12 years old at Screening will be randomized 1:1:1 double-blind to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo every 4 weeks during the 52-week Treatment Period. Randomization for the Main Efficacy Population will be stratified by type of background therapy (i.e., nusinersen or risdiplam) and age at initiation of SMN upregulator therapy (>=5 and <5).
• For the Exploratory Subpopulation, a maximum of 48 patients who are 13

through 21 years old at Screening will be randomized 2:1 double-blind to receive apitegromab 20 mg/kg or placebo every 4 weeks during the 52-week Treatment Period. Randomization for the Exploratory Subpopulation will be stratified by type of background therapy (i.e., nusinersen or risdiplam).

Study burden and risks

-The study lasts a total of approximately 76 weeks for patients.
-Additional hospital visits, additional physical tests, including a pregnancy test.
-A total of approximately 150ml of blood is taken. This amount is not a problem (for comparison: a blood donation means that 500 ml of blood is taken each time). Possible side effects of blood tests include fainting, soreness and tenderness at the injection site and, in rare cases, infection.
-If the study drug does not work for the patient, he/she may see an increase in his/her disease symptoms.

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

1. 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 patient's parent or legal guardian and patient's oral or written assent obtained, if applicable and in accordance with the regulatory and legal requirements of the participating location.
2. Males and females 2 through 21 years old at Screening
3. Estimated life expectancy >2 years from Screening
4. Documented diagnosis of 5q SMA
5. Diagnosed with later-onset SMA (i.e., Type 2 and Type 3 SMA) before receiving an approved SMN upregulator therapy (i.e., either nusinersen or risdiplam). 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.
6. Must be nonambulatory at Screening. Nonambulatory patients must be able to sit independently (sits up straight with head erect for at least 10 seconds; does not use arms or hands to balance body or support position) per WHO motor milestones at Screening
7. Receiving one background therapy for SMA (i.e., either nusinersen or risdiplam) for the time period specified below and anticipated to remain on that same treatment throughout the trial
a. If receiving the SMN upregulator therapy nusinersen, must have completed at least 10 months of dosing (i.e., completed the loading regimen and at least 2 maintenance doses) before Screening
b. If receiving the SMN upregulator therapy risdiplam, must have completed at least 6 months of dosing before Screening
8. Motor Function Score (HFMSE) >=10 and <=45 at the Screening Visit
9. No physical limitations that would prevent the patient from undergoing motor function outcome measures throughout the trial
10. Able to receive study drug infusions and provide blood samples through the use of a peripheral IV or a long-term IV access device that the patient has placed for reasons independent from the trial (i.e., for background medical care and not for the purpose of receiving apitegromab in the trial), throughout the trial
11. Able to adhere to the requirements of the protocol, including travel to the trial site and completing all trial procedures and trial visits
12. Females of childbearing potential must have a negative pregnancy test at Screening and agree to use at least 1 acceptable method of contraception throughout the trial and for 20 weeks after the last dose of study drug. Female

patients who are expected to have reached reproductive maturity by the end of the trial must agree to adhere to
trial-specific contraception requirements.

Exclusion criteria

1. Received ZOLGENSMA® (onasemnogene abeparvovec-xioi) at any time
2. Previous treatment with apitegromab
3. Prior history of severe hypersensitivity reaction or intolerance to SMN upregulator therapies
4. Prior history of a hypersensitivity reaction to a mAb or recombinant protein bearing an Fc domain (e.g., a soluble receptor-Fc fusion protein), apitegromab, or excipients of apitegromab
5. Require invasive ventilation or tracheostomy
6. Nutritional status that was not stable over the past 6 months and is not anticipated to be stable throughout the trial or medical necessity for a gastric/nasogastric feeding tube, where the majority of feeds are given by this route, as assessed by the Investigator
7. 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 motor function outcome measures, within 6 months before Screening or anticipated during the trial
8. Treatment with other investigational drugs in a clinical trial within 3 months or 5 half-lives, whichever is longer, before Screening
9. Use of valproic acid or hydroxyurea within 90 days before Screening
10. Use of therapies with potentially significant muscle effects (e.g., androgens, insulin like growth factor, growth hormone, systemic betaagonist, botulinum toxin, or muscle relaxants or muscle-enhancing supplements) or potentially significant neuromuscular effects (e.g., acetylcholinesterase inhibitors) other than approved SMN upregulator therapy within 60 days before Screening
11. Use of systemic corticosteroids within 60 days before Screening. Inhaled or topical steroids are allowed.
12. Any acute or comorbid condition interfering with the well-being of the patient within 7 days before Screening, including active systemic infection, the need for acute treatment, or inpatient observation due to any reason
13. Severe contractures (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) or scoliosis (general guideline for Grade 3) at Screening. Based on clinical judgment, any contractures or scoliosis present must be stable over the past 6 months, anticipated to be stable throughout the trial, and not prevent the patient from being evaluated on any motor function outcome measures throughout the trial.
14. Use of chronic daytime noninvasive ventilatory support for >16 hours daily

in the 2 weeks before dosing, or anticipated to regularly
receive such daytime ventilator support chronically throughout the trial
15. Pregnant or breastfeeding
16. Any other condition or clinically significant laboratory result or ECG
value that, in the opinion of the Investigator, may compromise safety or
compliance, would preclude the patient from successful completion of the trial,
or interfere with the interpretation of the results

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:	Completed
Start date (anticipated):	29-07-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Apitegromab
Generic name:	Apitegromab

Ethics review

Approved WMO Date:	10-03-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-06-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-07-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-08-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2021-005314-34-NL
CCMO	NL80453.028.22