An Observational Study in Participants with Ryanodine Receptor 1-Related Myopathies (RYR1-RM) to Determine Optimal Endpoint Measurements.

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Primary objective* To determine the extent to which muscle strength is affected in patients with RYR1-RM with autosomal dominantmutations and describe measurements over time.Secondary objectives* To determine the extent to which fatigue and physical...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON56922

Source
ToetsingOnline

Brief title
ARMGO RYR1-RM Endpoints

Condition

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

Synonym
muscle weakness and fatigue

Research involving
Human

Sponsors and support

Primary sponsor: ARMGO Pharma, Inc.
Source(s) of monetary or material Support: industry

Intervention

Keyword: Endpoints, RYR1-RM

Outcome measures

Primary outcome

The primary outcome measure is muscle strength assessment and change or variability in muscle strength over the duration of the study This will be tested using multiple methods, including Quantitative Muscle Assessment (QMA), Manual Muscle Test (MMT), and Hand Held Dynamometry (HHD). Additional tests for measuring strength including 10 meter walk test, 1-min sit-to-stand test and stair climb test will also be used in this study. Muscles to be measured are neck flexion, shoulder abduction, elbow flexion, knee extension and flexion strength. The study will essentially determine endpoints to take forward in further studies.

Secondary outcome

Secondary outcomes measures include:

• Fatigue physical function and physical activity will be measured using PROs.

• Demographics and clinical characteristics (medication use including current and prior medications, medical history, physical, neurological, and functional exam, height, weight, BMI, and vital

signs)

• Patient symptoms will be reported using a symptom diary that will be

completed by patients in their own words

detailing their main symptom,other symptoms as well as medications they are

currently taking.

Study description

Background summary

Ryanodine receptor isoform 1-related myopathies (RYR1-RM) are rare, slowly progressive neuromuscular diseases. They are the most common class of congenital myopathies caused by pathogenic variants in the ryanodine receptor isoform 1 (RYR1) gene and encompass a heterogeneous spectrum of histopathological and clinical subtypes. The RYR1-gene encodes a major skeletal muscle Ca2+ release channel - RyR1. RyR1 is embedded within the sarcoplasmic reticulum membrane of skeletal muscle and is a critical component needed for effective skeletal muscle excitation-contraction coupling. Mutations within the RYR1 gene result in chronic Ca2+ leak from the sarcoplasmic reticulum and primarily impair excitation-contraction coupling. Chronic Ca2+ leak into the sarcoplasm may lead to increased mitochondrial-related oxidative stress, RyR1 channel oxidation, cellular injury, leading to myopathy. Affected individuals present with mild to severe symptoms ranging from delayed motor milestones, proximal muscle weakness, hypotonia, impaired ambulation, joint contractures, and fatigue to scoliosis, ophthalmoplegia, and respiratory involvement. Although RYR1-RM has been associated with significant morbidities and early mortality, there is currently no approved treatment for this debilitating condition. Thus, there is a clear unmet need for therapies to treat RYR1-RM. Rycals® are a novel class of Ca2+ channel stabilizers that are currently in clinical development.
A RyR1 binding site was identified where the Rycal compound, ARM210 (S48168) binds cooperatively with adenosine triphosphate (ATP), stabilizes the closed state of the channel and prevents pathological pore opening. ARM210 (S48168) is expected to be a disease-modifying therapy for RYR1-RM patients whose only defect is leaky RyR1. ARM210 (S48168) has

completed Phase I clinical studies in healthy volunteers. ARM210 (S48168) is safe and well tolerated in single and multiple
dose studies and has now been tested in 7 patients with RYR1-RM. Before progressing to Phase II there is a need to define
appropriate endpoints. This non-interventional study plans to provide evidence to support the optimal endpoints for a Phase II
study.

Study objective

Primary objective
* To determine the extent to which muscle strength is affected in patients with RYR1-RM with autosomal dominant
mutations and describe measurements over time.

Secondary objectives
* To determine the extent to which fatigue and physical function is affected in patients with RYR1-RM with autosomal
dominant mutations.
* To describe the demographic and clinical characteristics of patients with RYR1-RM with autosomal dominant
mutations in the real-world setting.

Exploratory objective
* To evaluate the Syde® device for use in patients with RYR1-RM with autosomal dominant mutations

Study design

This is an observational, prospective, multi-centre study to assess muscle strength in participants with RYR1-RM with autosomal dominant mutations. The study will consist of up to 4 visits, each taking place approximately 30 days apart with the following windows of deviation to allow for flexibility in participant scheduling defined as follows: Screening Visit (0 days), Visit 1 (±3 days), Visit 2 (-14/ +3 days) and End of Study Visit (-14/ +3 days). Therefore, the length of time for a participant to complete all four visits would range from a minimum of 59 days to a maximum of 99 days. The overall duration of the study will be up to 9 months, from first data collection to reporting of results.

Intervention

Screening Visit (0 day)
* Informed consent;
* Inclusion/Exclusion (including MMT to assess muscle/motor function deficit, 10-MWT to assess ability to walk, and

FVC to assess pulmonary dysfunction);
* Demographics (medical records);
* Medical history (medical records) ;
* Medication use (medical records);
* Vital signs and ECG (medical records or primary data collection; note that FVC will be evaluated as part of the
assessment of the exclusion criteria);
* Strength measurements using QMA and HHD (note that MMT will be conducted at the start of the Screening Visit
as part of the assessment of the inclusion criteria);
* 1-Minute Sit-to-Stand Test;
* 4SCT;
* Full physical, neurological, and functional examination;
* PROMIS Questionnaires;
* IPAQ;
* Syde® device fitting;
* Symptom diary (initiation); and
* Adverse events (AE)/Serious adverse events (SAE).

Visit 1 (30 ± 3 days), Visit 2 (60 ± 3 days), and End of Study Visit (90 ± 3 days)
* Medication use (at Visit 1, Visit 2, and End of Study Visit);
* Strength measurements using QMA, HHD, and MMT (at Visit 1, Visit 2, and End of Study Visit);
* 10-MWT (at Visit 1, Visit 2, and End of Study Visit);
* 1-Minute Sit-to-Stand Test (at Visit 1, Visit 2, and End of Study Visit);
* 4SCT (at Visit 1, Visit 2, and End of Study Visit);
* PROMIS Questionnaires;
* IPAQ (at End of Study Visit);
* Full physical, neurological, and functional examination (at End of Study Visit);
* Syde® device removal (at Visit 1);
* Symptom Diary (patients will stop using the diary at End of Study Visit); and
* AE/SAE (at Visit 1, Visit 2, and End of Study Visit).

Study burden and risks

Physical risks following participation in the study are not anticipated.
This study involves strength measurements which should not pose a risk to subjects. However, they may experience discomfort and tiredness from carrying out the activities required for the physical assessment. Subjects will have the option to take short breaks between assessments if needed.
Wearing the Syde® device should also not pose any risks to subjects. They might feel some discomfort from wearing the device, but it is expected that this is no more uncomfortable than wearing a watch, but in this case around the ankles.
Taking part in the study will cost extra time to subjects.

Contacts

Public
ARMGO Pharma, Inc.

923 Saw Mill River Road PMB 260
Ardsley NY 10502
US
Scientific
ARMGO Pharma, Inc.

923 Saw Mill River Road PMB 260
Ardsley NY 10502
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Males and females aged 18 years and older at screening;
- Confirmed genetic diagnosis of RYR1-RM with autosomal dominant mutation and supporting clinical phenotype with demonstrable proximal weakness on at least one of the baseline study assessments;
- Evidence of at least one demonstrable muscle/motor function deficit assessed through Manual muscle Testing (MMT) and scored using the medical Research Council (MRC) Scale for muscle strength on physical examination;
- Able to walk 10 meters, with or without assistance - e.g. with a cane (assessed using the 10 Meter Walk Test);
- Willingness and ability to comply with scheduled visits and study procedures;
- Willingness to be fitted with the Syde device at Screening Visit (for inclusion in the exploratory objective analysis only); and

- Able to provide written informed consent and understand the study procedures in the informed consent form (ICF).

Exclusion criteria

- Severe pulmonary dysfunction at Screening (FVC < 40% predicted) or evidence of pulmonary exacerbation (note that pulmonary exacerbations refer to acute worsening respiratory symptoms resulting from a decline in lung function);
- Significant cognitive impairment in the judgement of the investigator who will be unable to follow the protocol;
- Patients with progressive neurological conditions (e.g. Parkinson's disease);
- Non-ambulant patients; or
- Pregnant woman.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-09-2024
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	30-07-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	15-10-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL85968.091.24