An Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, Biological Activity, and Systemic Exposure of ATYR1940 in Adult Patients with Facioscapulohumeral Muscular Dystrophy (FSHD)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON44009

Source
ToetsingOnline

Brief title
ATYR1940-C-005

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Facioscapulohumeral muscular dystrophy, genetic myopathy

Research involving

Human

Sponsors and support

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

Intervention

Keyword: ATYR1940, Extension Study, Genetic Myopathy, Muscular Dystrophies

Outcome measures

Primary outcome

Safety and tolerability will be evaluated by the following in all patients:

1. Change from baseline in physical examination, including neurological

examination.

2. Incidence of AEs, including serious and severe AEs.

3. Change from baseline in safety laboratory test results.

4. Change from baseline in electrocardiogram (ECG) findings.

5. Change from baseline in vital sign measurements and pulmonary evaluations

(pulmonary function tests and pulse oximetry).

6. Anti-drug antibody (ADA) titers and Jo-1 antibody levels.

7. Exploratory characterization of immune response to ATYR1940.

Secondary outcome

Muscle strength and function will be assessed by the following:

• Muscle strength, based on Quantitative muscle testing (QMT).

• Muscle strength, based on Manual muscle testing (MMT).

• Lower extremity muscle function based on the Vignos scale.

Quality of life will be assessed, based on the Individualized Neuromuscular Quality of Life (INQoL) questionnaire and the FSHD-specific Health Inventory (FSHD-HI) questionnaire. Additional measures of quality of life (e.g., sleep status) also will be explored.

The pharmacodynamic effects of ATYR1940 will be evaluated by the following:

• Muscle disease burden on lower extremity skeletal muscle MRI.

• Changes in FSHD-related inflammatory immune state in peripheral blood, as assessed by:

• Circulating immune proteins such as cytokines.

• Ex vivo inflammatory immune protein (including cytokines) release from peripheral blood mononuclear cells (PBMCs).

• Immunophenotyping (general and FSHD-specific) of circulating PBMCs.

Systemic exposure will be determined through PK sampling. As the data allow, PK parameters will be calculated from the drug concentration data using WinNonlin.

Study description

Background summary

FSHD is a rare, debilitating genetic myopathy. The primary clinical phenotype of FSHD patients is progressive skeletal muscle weakness which usually starts with muscles in the face and neck, and moves to the shoulder girdle, upper arms, trunk, and legs. As weakness progresses, musculoskeletal deformities (e.g., scapular winging, hyper-lordosis, and kyphoscoliosis) develop, and mobility becomes severely compromised. There are currently no pharmacological interventions for this disease worldwide.

ATYR1940 is a protein therapeutic candidate administered intravenously. This protein is identical to amino acids 2-506 of the human histidyl tRNA synthetase (HARS). HARS is a physiologically relevant modifier of muscle cell biology, and the ATYR1940 nonclinical data suggest that it may have therapeutic effect in patients with inflammatory muscle diseases, including FSHD, by modulating both immune and muscle cell responses.

Study objective

The objectives of this study are to:
• Evaluate the safety, tolerability, and immunogenicity of long-term treatment with intravenous (IV) ATYR1940 in adult patients with facioscapulohumeral muscular dystrophy (FSHD) previously enrolled in clinical study ATYR1940-C-002.
• Evaluate the effects of long-term ATYR1940 treatment on clinically relevant measures of muscle strength and function, including:
• Quantitative Muscle Testing (QMT); and
• Manual muscle testing (MMT), as determined by the Investigator
• Evaluate the effects of long-term ATYR1940 treatment on patient-reported quality of life (QoL).
• Evaluate the effects of long-term ATYR1940 treatment on muscle disease burden, based on skeletal muscle magnetic resonance imaging (MRI).
• Explore biological and pharmacodynamic (PD) changes in the inflammatory immune state in peripheral blood.
• Determine the long-term systemic exposure to ATYR1940 through pharmacokinetic (PK) sampling.

Study design

Study ATYR1940-C-005 is a multi-national, multi-center, open-label extension study designed to evaluate the long-term safety, effects on muscle, PD, and systemic exposure of ATYR1940 in adult patients with FSHD previously treated in the Protocol ATYR1940-C-002 (i.e., the parent study). This study will be conducted at the same study centers at which patients were enrolled in the parent study.

Patients who participated in >=Cohort 2 in the parent study, completed the double-blind treatment period in the parent study; in the Investigator*s opinion, demonstrated acceptable tolerability of study drug; are considered by the Investigator to be compliant with study drug and the study procedures; and do not meet any criterion for study drug discontinuation are eligible for participation in the current study, contingent upon Investigator and patient agreement to continue study drug treatment.

Patients may be treated with ATYR1940 under this protocol until ATYR1940 is approved or its development is discontinued, the study is closed by the Sponsor, or a criterion for study drug discontinuation is met.

Intervention

In the current study, all patients will receive ATYR1940 3.0 mg/kg administered via IV infusion over 90 minutes once weekly, unless it is determined by the Investigator in consultation with the Medical Monitor and Sponsor that a patient should receive a lower dose level from the Parent study and/or the infusion volume and dosing duration (e.g., infusion over 30 minutes) should be adjusted, as medically indicated. The treatment assignment in the parent study will remain blinded.

Study burden and risks

Foreseeable Benefits

The current study represents a long term extension study to the parent study, ATYR1940-C-002, a second clinical investigation of ATYR1940 in patients with facioscapulohumeral muscular dystrophy (FSHD). FSHD is a chronic condition that severely weakens skeletal muscles, significantly impairs mobility and interferes greatly with patients* daily functioning.

There are currently no specific treatments available for any form of FSHD disease; supportive therapy is the primary treatment, aimed at palliating the physical dysfunction, pain and fatigue. Considering the debilitating nature of the disease and the absence of specific therapy, there remains a pressing unmet medical need for an efficacious, safe and disease-specific treatment for FSHD.

Although there is no pharmacologic treatment for muscle disease in FSHD, both the dystrophic changes and the inflammatory process have been considered rational disease targets. Recent data in FSHD suggest that focusing on the inflammatory status of muscles in patients a priori in a clinical study could increase the likelihood of seeing an impact of an immune modulator on the disease.

ATYR 1940 is a recombinant protein having 100% identity to the first 506 amino acids of human cystolic histadyl-tRNA synthetase and is being developed as a treatment for rare myopathies with an immune component including genetic dystrophies.

Non-clinical studies in animals have shown that IV administered ATYR1940 attenuates immune disorder effectively in the dose range to be studied in humans. Non-clinical studies in immune cells isolated from the blood of healthy subjects have shown direct immune modulatory effects of ATYR1940. Taken together, ATYR1940 nonclinical data suggest that it may have therapeutic effect in patients with inflammatory muscle diseases, including FSHD, by modulating both immune and muscle cell responses.

The first in human clinical trial in healthy volunteers demonstrated the safety and tolerability of single ascending doses of ATYR1940, and additional multiple dosing in patients supports the proposed multiple-dose study of ATYR1940 in patients.

However, as with any clinical trial of an investigational agent, it is unsure whether the study drug will improve the symptoms of the subjects or alter the disease state of those participating in the trial. The results of this trial will benefit future research in FSHD.

Possible Risks Based on Experience in Clinical Studies

To date, more than 40 subjects (24 healthy subjects and approximately 16 subjects with FSHD) have received at least one dose of ATYR1940 via infusion ranging from 0.1 to 3.0 mg/kg. Overall, ATYR1940 has been well-tolerated.

In a study completed with healthy volunteers, subjects were given a single dose of ATYR1940 up to 3.0 mg/kg. The most common adverse events reported were dizziness and headache in 13% of subjects and abdominal distension (feeling bloated), fatigue, nasopharyngitis (common cold), and sore throat in 8% of subjects.

In ongoing studies, patients with FSHD were treated with ATYR1940 at weekly doses via infusion of 0.3 and 1.0 mg/kg for 4 weeks and 3.0 mg/kg for 12 weeks. The most common adverse events reported were back pain in 27% of subjects, joint pain, cough, and headache in 20% of subjects, and muscle pain, nausea, and presyncope (feeling faint, lightheaded) in 13% of subjects. All events were mild or moderate in intensity and all were considered non-serious except for one event described below. Some patients showed abnormalities in their blood and urine results, however, these were all considered mild in intensity, not clinically significant, and unrelated to ATYR1940.

Generalized infusion related reactions have been reported in patients treated weekly with 3.0 mg/kg of ATYR1940 (via 30-minute infusion) for 6 or more weeks. One generalized infusion related reaction was considered to be serious. In all cases, symptoms resolved after stopping the infusion and in some instances, treating with medication and IV fluids. ATYR1940 dosing was permanently discontinued in all patients who experienced an IRR.

Signs and symptoms of the observed generalized infusion related reactions occurred during or after the infusion and included: flushing (temporary redness of the skin, sometimes accompanied by feeling hot), sweating, itchiness, a tingling sensation on the lips, lightheadedness, fainting, shortness of breath, chills, low heart rate and/or blood pressure, and/or headache. These patients also had increases in their Jo-1 antibody levels while participating in the clinical studies, but the relationship between the Jo-1 Ab increases and the generalized infusion related reaction is unknown at this time.

Patients will be monitored for these and other symptoms that may indicate a generalized IRR during study drug infusions. There have been stopping rules added to the study to ensure patient safety: patients will have study drug discontinued and will not receive further drug if an infusion reaction occurs or if their Jo-1 antibody level rises above 1.5 U/L.

In animal studies, some animals given ATYR1940 twice weekly, at doses significantly higher than will be used in this trial, had anti-drug antibodies detected and showed symptoms including skin changes, difficulty breathing and decreased physical activity levels, minutes after ATYR1940 IV administration. The symptoms were temporary in the majority of animals and there was no evidence of the chronic lung or muscle damage. In a small percentage of animals treated at the highest dose levels, death or severe illness requiring euthanasia occurred acutely in the setting of these symptoms.

There is a small risk that a patient could develop very high levels of anti-drug antibodies during the course of the study that could alter how the protein works in the body and/or could cause an illness called anti-synthetase syndrome. ATYR1940 may increase the risk of developing this illness.

Patients will be monitored regularly for lung function and for anti-drug antibody levels, and as stated above, will be discontinued if the Jo-1 Ab level rises above a threshold that is much less than what is considered positive for anti-synthetase syndrome (7 U/L is considered equivocal, >=10 U/L positive).

ATYR1940 has not yet been tested to see if it affects pregnancy. Therefore, patients should not become pregnant, or father a baby, while on this study. Women should not breastfeed a baby while in this study. Men should not donate sperm while in this study.

Possible risks and adverse effects related to the study procedures

• Blood sample collection: It may be painful when blood is drawn from the vein. Some people get dizzy or faint from a blood draw. The patient could also get an infection (rare), or have bleeding, redness, or bruising at the skin puncture.
• ECG: The sticky pads used for these tests may cause skin irritation.
• Spirometry: The patient may feel the need to cough or you may feel short of breath during or after the test.
• MRI: There are no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. However, there are important safety concerns to consider before performing or undergoing an MRI scan (for example patients cannot wear anything with metal and precautions are needed if they have artificial limbs or a pacemaker). The patient may also feel some discomfort or anxiety when lying inside of the MRI scanner.

For further information about risks and side effects, please refer to the patient information leaflet.

Patients will be monitored for safety, including respiratory events and immune responses, throughout the study. A Data Monitoring Board will review all safety data on an ongoing basis. Unforeseen/unwanted events will be taken care of by the study staff at all sites, which are experienced in handling patients with FSHD and in conducting similar clinical trials.

Based on the data available to date and the planned safety monitoring, as well as the high unmet need for treatments in FSHD, the overall risk-benefit balance for this trial is considered to be acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Enrolled in >=Cohort 2 and completed the double-blind treatment period in the parent

study.;2. Demonstrated, in the Investigator*s opinion, acceptable tolerability of study drug.;3. In the Investigator*s opinion, patient has shown acceptable compliance with study drug and the study procedures in the parent study and is willing and able to comply with all procedures in the current study.;4. Is, in the opinion of the Investigator and Sponsor, a suitable candidate for continued study drug treatment.;5. Provided written informed consent after the nature of the study has been explained and prior to the performance of any research-related procedures.

Exclusion criteria

1. At any time during participation in the parent study, met a study drug discontinuation criterion, including, but not limited to:;a. Jo-1 Ab levels >=1.5 U/mL.;b. Clinical evidence of a generalized infusion-related reaction (IRR).;c. Clinical evidence of a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) >=1.5 U/mL;d. Pregnancy.;e. Progression of disease that, in the opinion of the Investigator, precluded further participation in the study.;f. Withdrawal of consent.;g. Other findings that, at the discretion of the Investigator and/or Sponsor, indicated that study drug administration should be discontinued.;2. Is expected to require treatment with curcumin or systemic albuterol (intermittent inhaled albuterol is permissible) during study participation; or use of a product that putatively enhances muscle growth (e.g., insulin-like growth factor, growth hormone) or activity (e.g., Coenzyme Q, Coenzyme A, creatine, L-carnitine) on a chronic basis; or statin treatment initiation or significant adjustment to statin regimen (stable, chronic statin use is permissible).;3. Planned to receive any vaccination during study participation.;4. Abnormal baseline findings, medical condition(s), or laboratory findings that, in the Investigator*s opinion, might jeopardize the patient's safety or decrease the chance of obtaining satisfactory data needed to achieve the objectives of the study.;5. Evidence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, metabolic, dermatological, or gastrointestinal disease, or has a condition that requires immediate surgical intervention or other treatment or may not allow safe participation.;6. If female and of childbearing potential (premenopausal and not surgically sterile), has a positive pregnancy test at entry or is unwilling to use contraception from the time of entry through the 1-month Follow-up visit. Acceptable methods of birth control include abstinence, barrier methods, hormones, or intra-uterine device. ;7. If male, is unwilling to use a condom plus spermicide during sexual intercourse from the time of entry through the 1 month Follow-up visit.

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-08-2015
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available
Generic name:	not available

Ethics review

Approved WMO Date:	22-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-02-2016

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-07-2016
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
EudraCT	EUCTR2015-001912-36-NL
CCMO	NL53832.091.15