A Placebo-Controlled, Randomized, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Biological Activity of ATYR1940 in Adult Patients with Molecularly Defined Genetic Muscular Dystrophies

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Primary objective:Evaluate the safety, tolerability, pharmacokinetics (PK), and immunogenicity of multiple doses of intravenous (IV) ATYR1940 in adults 18 to 65 years of age, inclusive, with FSHDSecondary objective:Explore pharmacodynamic (PD)...

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

Summary

ID

NL-OMON42284

Source
ToetsingOnline

Brief title
ATYR1940-C-002

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, FSHD, Genetic Myopathy, Muscular Dystrophies

Outcome measures

Primary outcome

Safety and tolerability will be evaluated by the following:

• Change from Baseline of physical examination.

• Incidence of AEs.

• Change from Baseline in safety laboratory test results.

• Change from Baseline in ECG findings.

• Change from Baseline in vital sign measurements and pulmonary evaluations.

• Antibody test results.

• Incidence of infusion reactions and infusion site examination findings.

The following PK parameters will be determined or calculated from the drug

concentration time data as follows using WinNonlin:

• Standard PK parameters (Cmax, tmax, t1/2, etc).

Secondary outcome

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

• Changes in FSHD-related inflammatory immune state in peripheral blood and

muscle.

• Changes in the following clinical parameters.

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

Primary objective:
Evaluate the safety, tolerability, pharmacokinetics (PK), and immunogenicity of multiple doses of intravenous (IV) ATYR1940 in adults 18 to 65 years of age, inclusive, with FSHD

Secondary objective:
Explore pharmacodynamic (PD) changes in the following biological parameters:
• FSHD-related inflammatory immune responses in skeletal muscle, as assessed by quantitative magnetic resonance imaging (MRI).
• 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-related) of circulating PBMCs.

Explore PD changes in the following clinical parameters:
• Manual muscle testing (MMT), as determined by the Investigator.
• Individualized Neuromuscular Quality of Life (INQoL) instrument, as determined by the patient.

Study design

Study ATYR1940-C-002 is a multi-national, multi-center, double-blind, randomized, placebo-controlled, ascending dose study.

After enrollment, patients will enter the 1-week single-blind placebo period during which all patients will receive a single 30-minute IV infusion of placebo. Thereafter, patients will enter the double-blind treatment period and will receive 30-minute IV infusions of Study Drug (ATYR1940 or placebo) according to their random treatment assignment.

During treatment, patients are to attend study center visits weekly. Patients in Cohorts 1 and 2 also are to attend a visit mid-week after the fourth Study Drug dose. After completion of the 1-week single-blind placebo period and the double-blind treatment period, all patients are to attend a follow-up visit 1 week after the last Study Drug dose. After completion of the 1-week follow-up visit, patients are to attend a follow-up visit 1 month after the last Study Drug dose. Additionally, patients will also attend a follow-up safety visit 3 months after the last Study Drug dose; the 3-month Follow-up visit is considered the End of Study (EOS) visit.

Intervention

During the single-blind placebo period, all patients will receive placebo on Day 1 via a 30-minute IV infusion.

During the double-blind treatment period, patients will receive Study Drug (ATYR1940 or placebo) according to the dose cohort in which they are enrolled and their treatment assignment. There is no adjustment to dose permitted in this study.

During the double-blind treatment period, Study Drug will be administered weekly for the duration of the double-blind treatment period (i.e., 4 or 12 weeks). Study drug will be administered via a 30-minute IV infusion. For the preparation of the mg/kg ATYR1940 dose, the patient's weight during Screening will be used.

Study burden and risks

Based on the nonclinical and clinical data available to date and the planned safety monitoring, the overall risk-benefit balance for this trial is considered to be acceptable.

Foreseeable benefits

The current study represents the first clinical investigation of ATYR1940 in patients with FSHD.

There currently is no pharmacologic treatment for muscle disease in FSHD. However, 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.

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.

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 and adverse effects related to ATYR1940

ATYR1940 has been given to 24 healthy people as well as animals. Possible risks and side effects based on human and animal studies are detailed below; however, there may be other risks and side effects that are not yet known.

• Risks observed in animals at a higher dose
o Difficulty breathing
o Development of anti-drug antibodies

• Risks observed in healthy volunteers
o Nervous system disorders: including single cases of dizziness, headache, and somnolence (sleepiness)
o Development of anti-drug antibodies (proteins that could make the drug inactive or cause illness): There is a risk that the patient will develop antibodies during the study, as a result of which the effect on the antibody in the body can change how the protein works in the body and/or could cause an illness that also occurs, although very rarely in the general population (in people not taking ATYR1940). This illness, called *anti-synthetase syndrome* is very rare and starts with skin signs (such as rash, cracking and scaling), joint pains and lung signs (dry cough and breathlessness), as well as muscle inflammation. There is also a risk of serious lung damage in this syndrome and worsening of muscle damage. The possibility exists that ATYR1940 may increase the risk of developing this syndrome especially in the setting of very high levels of anti-drug antibodies to ATYR1940.

Reproductive Risks

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.
• Chest X-ray: There is a low amount of exposure to radiation from a chest X-ray. The amount of radiation that the patient is exposed to is lower than what he/she is exposed to through natural sources of radiation in the environment.
• 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 DSMB will review all safety data prior to escalating to the next dose. 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.

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. Patient is a male or female aged 18 to 65 years, inclusive.;2. Patient has an established, genetically-confirmed, diagnosis of FSHD with clinical findings meeting existing criteria.;3. Patient has provided written informed consent after the nature of the study has been explained and prior to the performance of any research-related procedures.;4. Cohorts >=2 only: Patient has imaging findings meeting defined criteria for muscle inflammation in at least 1 skeletal muscle (as per MRI Procedural Manual).

Exclusion criteria

1. Patient is currently receiving treatment with an immunomodulatory agent or has a history of such treatment, including targeted biological therapies (e.g., etanercept, omalizumab) within the 3 months before Baseline; corticosteroids within 4 weeks before Baseline; or high-dose non-steroidal anti-inflammatory agents (NSAIDs) (either chronic or intermittent) within 2 weeks before Baseline.;2. Patient has evidence of an alternative diagnosis other than FSHD, based on prior muscle biopsy or genetic test findings.;3. Patient has a presumptive diagnosis of FSHD, based on clinical assessment, but does not yet have genetic confirmation of the diagnosis.;4. Patient has a history of obstructive or restrictive lung disease (including interstitial lung disease, pulmonary fibrosis, or asthma), or evidence for interstitial lung disease on Screening chest radiograph.;5. Patient has a history of anti-synthetase syndrome, prior Jo-1 antibody (Ab)-positivity, or has a positive or equivocally positive Jo 1 Ab test result during Screening.;6. Patient has symptomatic cardiomyopathy or severe cardiac arrhythmia that may, in the Investigator*s opinion, limit the patient*s ability to complete the study protocol.;7. Patient has 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.;8. Patient has used any investigational product or device (other than a mobility assistance device) within 30 days before Baseline.;9. Patient underwent muscle biopsy within 30 days before Baseline.;10. If female and of childbearing potential (premenopausal and not surgically sterile), patient has a positive pregnancy test at Screening or is unwilling to use contraception.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-10-2014
Enrollment:	16
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	03-06-2014
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-06-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-09-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-09-2015
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	EUCTR2014-001753-17-NL
CCMO	NL49110.091.14