An Open-Label Pilot Study of Losmapimod to Evaluate the Safety, Tolerability, and Changes in Biomarker and Clinical Outcome Assessments in Subjects With Facioscapulohumeral Muscular Dystrophy 1 (FSHD1) with Extension

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This study has been transitioned to CTIS with ID 2024-512736-29-00 check the CTIS register for the current data. Primary Objective1. To evaluate the safety and tolerability of long-term dosing of losmapimod tablets in subjects with FSHD1Secondary...

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

Summary

ID

NL-OMON49538

Source
ToetsingOnline

Brief title
Open-Label study of Losmapimod for FSHD1

Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders

Synonym

FSHD, Muscle disease

Research involving
Human

Sponsors and support

Primary sponsor: Fulcrum Therapeutics
Source(s) of monetary or material Support: Fulcrum Therapeutics

Intervention

Keyword: FSHD, Losmapimod, Safety, Treatment

Outcome measures

Primary outcome

Assessment of safety and tolerability based on adverse events (AEs), serious adverse events (SAEs), clinically significant laboratory test results, electrocardiograms (ECGs), and vital signs (safety endpoint)

Extension:

The primary endpoint is the assessment of the efficacy of treatment with losmapimod as evaluated by skeletal muscle echogenicity by ultrasound (selected muscles).

Secondary outcome

Change from baseline in pHSP27 and ratio of pHSP27/total HSP27 as measured by sorbitol stimulated peripheral whole blood and change from baseline in the ratio of pHSP27/total HSP27 in muscle (PD endpoint) and concentration losmapimod in blood and muscle (PK endpoint).

Exploratoty Endpoints:

Changes from baseline during the dosing period in the following:

1. DUX4 activity by quantitative polymerase chain reaction (qPCR) of skeletal muscle using a subset of DUX4 regulated gene transcripts
2. Other disease transcripts by qPCR of skeletal muscle
3. Skeletal muscle lean tissue volume by whole-body MRI
4. Skeletal muscle tissue replacement by fat using whole-body MRI
5. Skeletal muscle echogenicity by ultrasound (selected muscles)
6. Reachable Work Space (RWS) with and without weights
7. Ambulatory function by classic and FSHD-optimised TUG
8. Physical function by Motor Function Measure (MFM) domain 1
9. Muscle strength by quantitative manual dynamometry
10. Disease impact by subject report using FSHD-Rasch-built Overall Disability Scale (FSHD RODS)
11. Disease impact by subject report using FSHD-HI
12. Disease impact by subject report using Patient Global Impression of Change (PGIC)
13. Upper and lower limb mobility in the outpatient setting using wearables
14. Change in ambulation as measured by the 6-minute walking test (6-MWT)
15. Change in lung ventilatory function as measured by Spirometry

Extension:

Secondary Endpoints

1. Assessment of the efficacy of treatment with losmapimod as evaluated by whole body skeletal muscle MRI parameters.

2. Assessment of safety and tolerability based on AEs, SAEs, clinically significant laboratory test results, ECGs, and vital signs (safety endpoint).

3. Changes from baseline during treatment in pHSP27 and the ratio of pHSP27/total HSP27 as measured by sorbitol stimulated peripheral whole blood (pharmacodynamic [PD] endpoint).

Exploratory Endpoints

1. RWS with and without weights

2. Ambulatory function by classic and FSHD-optimised TUG

3. Physical function by MFM domain 1

4. Muscle strength by quantitative manual dynamometry

5. Muscle strength by manual muscle testing (MMT)

6. Disease impact by subject report using FSHD-RODS

7. Disease impact by subject report using FSHD-HI

8. Disease impact by subject report using PGIC

9. Change in ambulation as measured by the 6-minute walking test (6-MWT)

10. Change in lung ventilatory function as measured by Spirometry

Study description

Background summary

Facioscapulohumeral muscular dystrophy is a genetic muscular disorder that affects 1 in 20,000 people with currently no curative treatment. Aberrant expression of the double homeobox 4 (DUX4) program drives FSHD pathology and is due to genetic deletion of the D4Z4 repeat on chromosome 4q35 in FSHD1. The end result of DUX4 activity is myofibre death with replacement of skeletal muscle by fat, resulting in a clinical manifestation of progressive loss of strength and accumulation of physical disability. Losmapimod is a p38α/β MAP kinase inhibitor that has been shown to reduce DUX4 activity and expression of the DUX4 gene transcript pathway in preclinical studies. The therapeutic hypothesis for Fulcrum Therapeutic*s clinical development program is that treatment of FSHD with losmapimod will slow or arrest disease progression by reducing aberrant DUX4 expression via inhibition of p38α/β MAP kinase.

Study objective

This study has been transitioned to CTIS with ID 2024-512736-29-00 check the CTIS register for the current data.

Primary Objective
1. To evaluate the safety and tolerability of long-term dosing of losmapimod tablets in subjects with FSHD1

Secondary Objectives
1. To assess target engagement of losmapimod tablets in blood and skeletal muscle over long term dosing
2. To evaluate repeated dose PK of losmapimod tablets in subjects with FSHD1

Exploratory Objectives
1. To evaluate on-treatment change in target engagement and DUX4 activity and other disease transcripts in skeletal muscle needle biopsy
2. To evaluate on-treatment change in skeletal muscle by imaging biomarkers
3. To evaluate on-treatment change in skeletal muscle function by clinical outcome assessments
4. To evaluate on-treatment change in upper and lower limb mobility in the outpatient setting
5. To evaluate on-treatment change in lung ventilatory function
6. To evaluate on treatment change in circulating proteins associated with DUX4 expression or muscle injury or repair

Extension Objectives

Primary Objective
1. To evaluate on-treatment change in skeletal muscle by ultrasound

Secondary Objectives

1. To evaluate on-treatment change in skeletal muscle by imaging biomarkers
2. To evaluate the safety and tolerability of long-term dosing of losmapimod in subjects with FSHD1
3. To evaluate changes from baseline during treatment in pHSP27 and the ratio of pHSP27/total HSP27 as measured by sorbitol stimulated peripheral whole blood (pharmacodynamic [PD] endpoint)

Exploratory Objectives
1. To evaluate on-treatment change in skeletal muscle function by clinical outcome assessments
2. To evaluate on-treatment change in lung ventilatory function
3. To evaluate on-treatment change in circulating proteins associated with DUX4 expression or muscle injury or repair

Study design

This study is open-label study. All subjects will be evaluated during an 8-week pre-treatment period to establish pre-treatment baseline assessments. All subjects will then be treated with losmapimod from Visit 4 through Visit 9 and assessed at relatively regular intervals for change from pre-treatment baseline assessments. A follow-up visit will be scheduled 4 weeks after the last dose.

Extension:
All subjects who completed the OLS study are allowed to enroll in the extension part of this study. Participants are able to continu dosing with losampimod. Subjects will need to come to the Radboudumc every 12 weeks for assessments for efficacy, safety and exploration of biomarkers. This extension will continu until 1) participants want to stop, 2) the drug has been accepted on the market, 3) Fulcrum stops the study because losmapimod shows no efficacy.

Study burden and risks

Participation in this study does not mean that the clinical symptoms, progression of disease, or underlying cause of FSHD1 will be improved or cured. Subjects may experience side effects or complications from the study treatment, as well as AEs and discomforts from the study assessments. Side effects of the investigational product include headache, fatigue, nasopharyngitis, dizziness, and back pain. There are currently no expected safety risks of the study drug.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1.FSHD1 subjects age 18-65 years., 2.Subject will sign and date an informed consent form (ICF)., 3.3. Subjects will have a confirmed diagnosis of FSHD1 with 1 to 9 repeats via assessment of the size of the D4Z4 array on chromosome 4 using the calculator provided by the sponsor. Genetic confirmation must be obtained prior to the screening MRI and baseline muscle biopsy; genetic confirmation can come from previous testing if verified with appropriate documentation. Due to stable transmission of repeat sizes within families, subjects with a clinical diagnosis of FSHD who have a first degree relative with a genetically confirmed diagnosis of FSHD1 may be entered into the study for screening and MRI. During screening, a confirmatory genetic diagnosis is conducted. If genetic testing during screening is necessary, the 4-week screening window will not start until the results are obtained and verified by the principal investigator. , 4.Subject will be willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, scheduled needle muscle biopsies, and other study procedures., 5.Male or female subjects:, a.A female subject is eligible to participate if she is of non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea or if of childbearing potential

is using a highly effective method for avoidance of pregnancy (refer to Section 5.5) for the duration of the clinical trial and until 90 days following the last dose. The decision to include or exclude women of childbearing potential may be made at the discretion of the investigator and in accordance with local practice in relation to adequate contraception., b.Male subjects must agree to use one of the contraception methods listed in Section 5.5. This criterion must be followed from the time of the first dose of study medication until 90 days after the last study drug dose., 6. Subject has a Clinical Severity Score between 2 and 4 on Ricci*s scale (scale range is from 0 to 5). Patients that use a wheelchair or walker for any activity are not permitted to enroll in the study., 7. Subject commitment to complete the 2 visits for skeletal muscle needle biopsy and all visits for whole body MRI., 8. Subject is able to complete the RWS, TUG, and FSHD PROs (FSHD-RODS and FSHD HI) at the screening visit., 9. Subject has an MRI-eligible muscle for biopsy as determined by the central reader.

Exclusion criteria

1. Subject has a history of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. This may include, but is not limited to, history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; clinically significant history of mental disease; and history of cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)., 2. Subject has a known or clinically suspected infection with human immunodeficiency virus or hepatitis B or C viruses., 3. Subject has current clinically significant liver or kidney dysfunction., 4. Subject screens positive for hepatitis B surface antigen, hepatitis C virus (HCV) antibody, or antibodies against human immunodeficiency viruses 1 and 2 (HIV 1/HIV 2 antibodies)., 5. Subject has any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy, or other gastrointestinal tract surgery, except appendectomy)., 6. Subject has a standard 12-lead ECG demonstrating QT interval by Fredericia (QTcF) >450 msec for male subjects and QTcF >470 msec for female subjects at Screening. If QTcF exceeds 450 msec for males or 470 msec for females, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject*s eligibility., 7. Subject has a history of cardiac dysrhythmias requiring anti-arrhythmia treatment(s); or history or evidence of abnormal ECGs that, in the opinion of the investigator or Medical Monitor, would preclude the subject*s participation in the study., 8. Male subject has a female partner who is planning to become pregnant during the study or within 90 days after the last study drug dose., 9. Subject has donated blood (of approximately 1 pint [500 mL] or more) or has had any significant loss of blood within 90 days

before the first study drug dose, as determined by the investigator., 10. Vaccination with a live attenuated vaccine within 6 weeks of randomization., 11. Subject has a history of alcohol, analgesic/opioid, and/or illicit drug abuse as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, in the last 6 months before screening, or a positive test for drugs of abuse at screening. 12. Subject has participated in a clinical trial in which they have received an investigational product within the following time period prior to enrolment in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever was longer)., 13. For subjects that are on drug(s) or supplements that may affect muscle function as determined by the treating physician or included in the list of drugs presented in Appendix 15.1: subjects must be on a stable dose of that drug(s) or supplement for at least 3 months prior to enrolment in the study and remain on that stable dose for the duration of the study (list of drugs presented in Appendix 15.1). Changes to the dose or treatment discontinuation during the study can only be done for strict medical reasons by the treating physician with clear documentation and notification to the sponsor., 14. Subject has a history of sensitivity to any of the study medications or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicated their participation., 15. Female subject is pregnant as determined by positive urine human Chorionic Gonadotropin test at Screening or prior to dosing., 16. Female subject is lactating., 17. Subject is unwilling or unable to follow the procedures outlined in the protocol., 18. Subject has any contraindication for MRI (including severe claustrophobia and any shrapnel or metal implants in the body that are not MRI compatible)., 19. Subject was mentally or legally incapacitated up to 2 years prior to enrolment., 20. Subject has abnormal laboratory results indicative of any significant medical disease that, in the opinion of the investigator or the medical monitor, would preclude the subject*s participation in the study., 21. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site., 22. Subject has taken any anticoagulants for at least 1 month and anti-platelet agents for at least 1 week before each muscle biopsy. Such agents are prohibited, as they increase the risk of hematomas following skeletal muscle needle biopsy.

Study design

Design

Study phase: 2

Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-08-2019
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Losmapimod
Generic name:	Not available

Ethics review

Approved WMO Date:	24-04-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-08-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	10-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2024
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
EU-CTR	CTIS2024-512736-29-00
EudraCT	EUCTR2019-001006-20-NL
ClinicalTrials.gov	NCT04004000
CCMO	NL69446.091.19