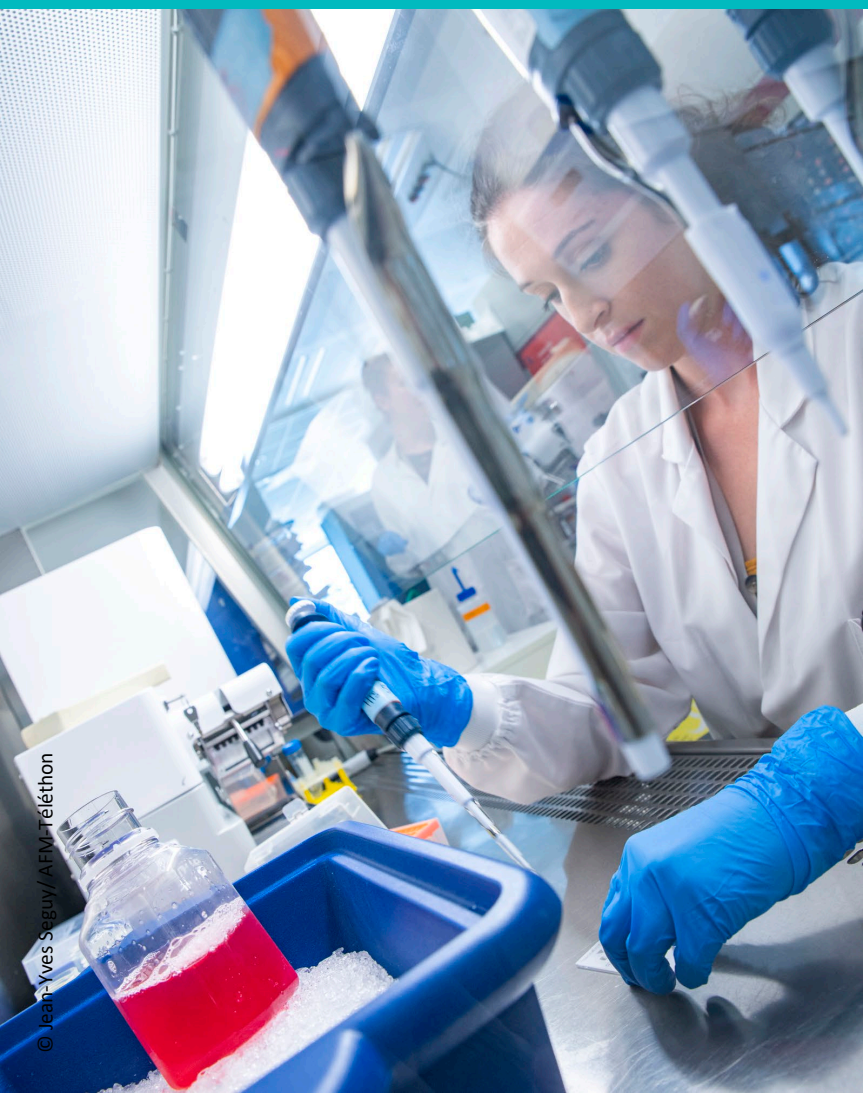
MAY 2025

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2025 in facioscapulohumeral muscular dystrophy



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This document, published to coincide with the AFM-Téléthon General Meeting 2025, presents a selection of FSHD research news stories from the past year (ongoing studies and clinical trials, scientific and medical publications...).

AFMTÉLÉTHON
INNOVER POUR GUERIR

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3 Highlights from the past 12 months

Losmapimod was unconvincing...

Last September, some disappointing news was announced for facioscapulohumeral muscular dystrophy (FSHD). **Losmapimod**, a drug candidate which was in the furthest stage of development in clinical trials (phase III), ultimately failed to demonstrate positive efficacy results. The pharmaceutical company Fulcrum Therapeutics decided to suspend its development.

...but many more clinical trials and observational studies have started recently

No fewer than 12 new clinical trials and observational studies in FSHD are listed as having started or preparing to since the beginning of 2024 on ClinicalTrials.gov, the most comprehensive clinical trials database in the world. These include clinical trials of two drug candidates: **ARO-DUX4** for blocking DUX4, and **satralizumab** for reducing inflammation.
A new trial of **clenbuterol**, a drug that has already been approved for the treatment of a chronic respiratory disease which reduces *DUX4* expression in cell models of FSHD, is currently in preparation and could be starting soon in the United States.

A new natural history study provides valuable insights into the disease

A natural history study of FSHD conducted in the Netherlands involving 154 adult patients with an average age of 51 who were monitored for five years showed **a slow progression of the disease.** These findings mean that clinical trial protocols need to be updated, for example, by:

- extending their durations (currently they last two years on average),
- using more sensitive outcome measures.

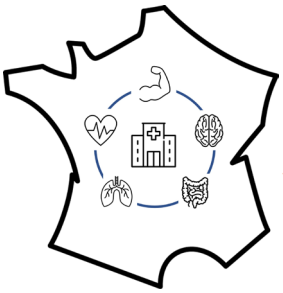
Facioscapulohumeral muscular dystrophy — FSHD

FSHD is a genetic muscle disorder (myopathy) characterised by muscle wasting (atrophy) and muscle weakness which typically begin in the upper body (face, arms and shoulders) and later affect the torso and legs.

Common symptoms

- **Muscle symptoms** may include weakness and wasting of the face (facio), shoulder (scapulo), arm (humeral), chest, abdominal, leg and dorsiflexor muscles (which lift up the toes).
- **Non-muscle symptoms** may include hearing loss, retinal vascular disease, chronic pain and severe fatigue.
- Symptoms are often **asymmetric** (different on both sides of the body) and vary considerably from person to person, even within the same family.

Management and treatment



- **Multidisciplinary treatment** of symptoms (particularly orthopaedic) at specialist centres and rehabilitative care facilities (physiotherapy, occupational therapy...).
- Preventing complications.
- Improving quality of life.

Regular, moderate exercise (walking, swimming, cycling...) helps improve wellbeing and reduce fatigue.

Diagnosis

Clinical diagnosis

Clinical examination by a doctor:
to look for asymmetric muscle involvement (face, shoulders and arms)

Genetic diagnosis

Blood test or muscle biopsy:
to look for a decrease in the number of repeats in the D4Z4 region on chromosome 4 and to identify permissive copies of chromosome 4

A few statistics

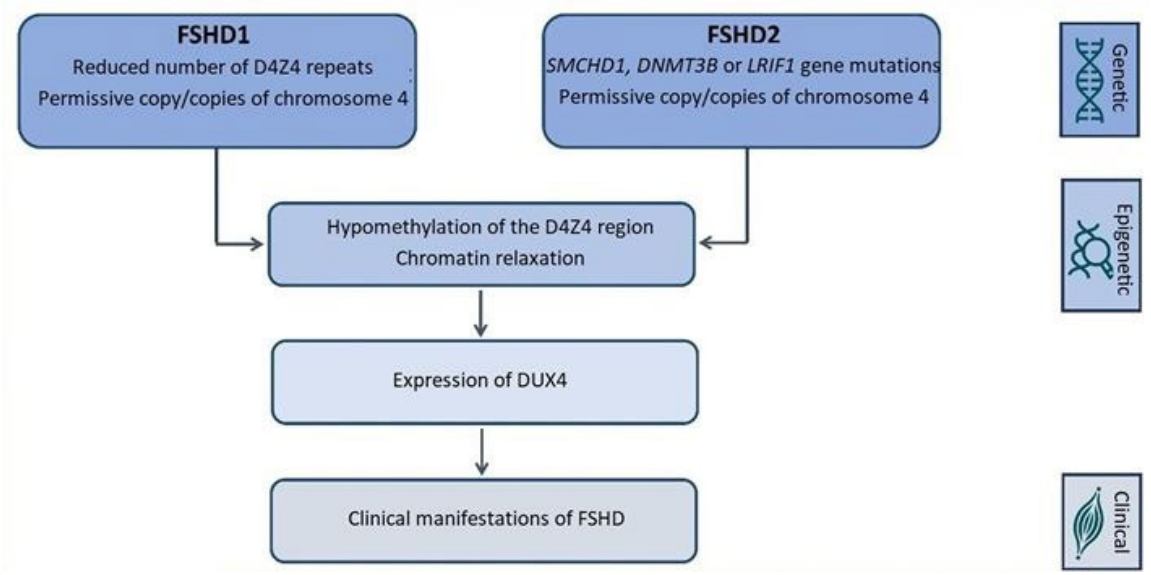
5 to 12 people in every 100,000 have FSHD

123 scientific articles published between April 2024 and April 2025 *(PubMed)*

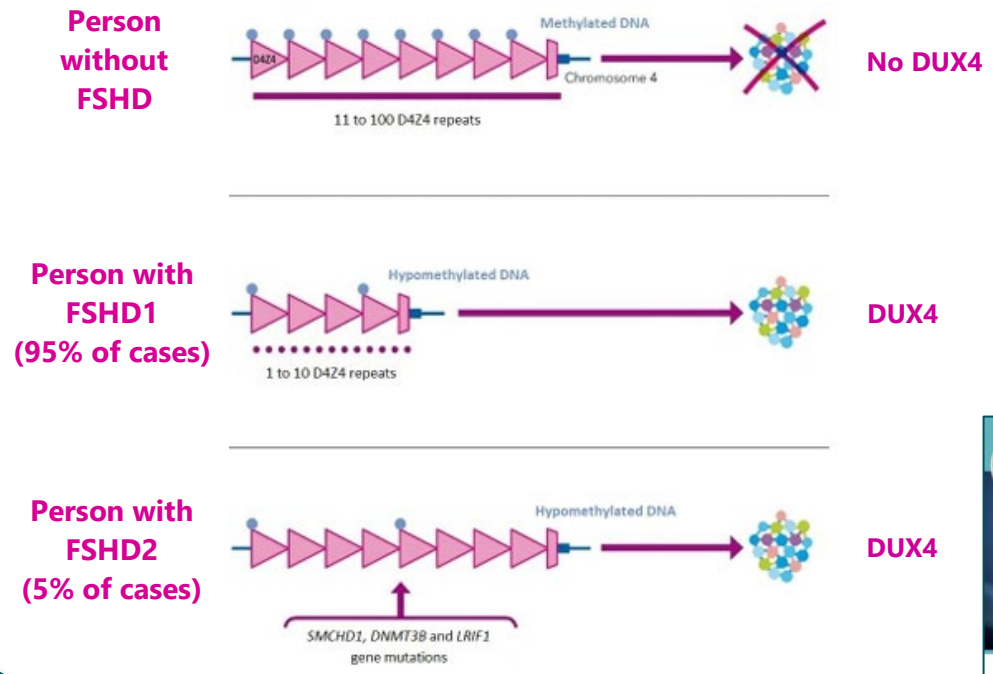
32 clinical trials including 7 in France *(ClinicalTrials.gov 31/03/2025)*

FSHD1 and FSHD2

- There are two types of FSHD which are **clinically similar but genetically different.**



- In FSHD1 and FSHD2, **the *DUX4* gene is abnormally expressed** in muscle.
- It codes for the DUX4 protein which participates in the inflammation and degradation of muscle fibres by activating a cascade of other genes.

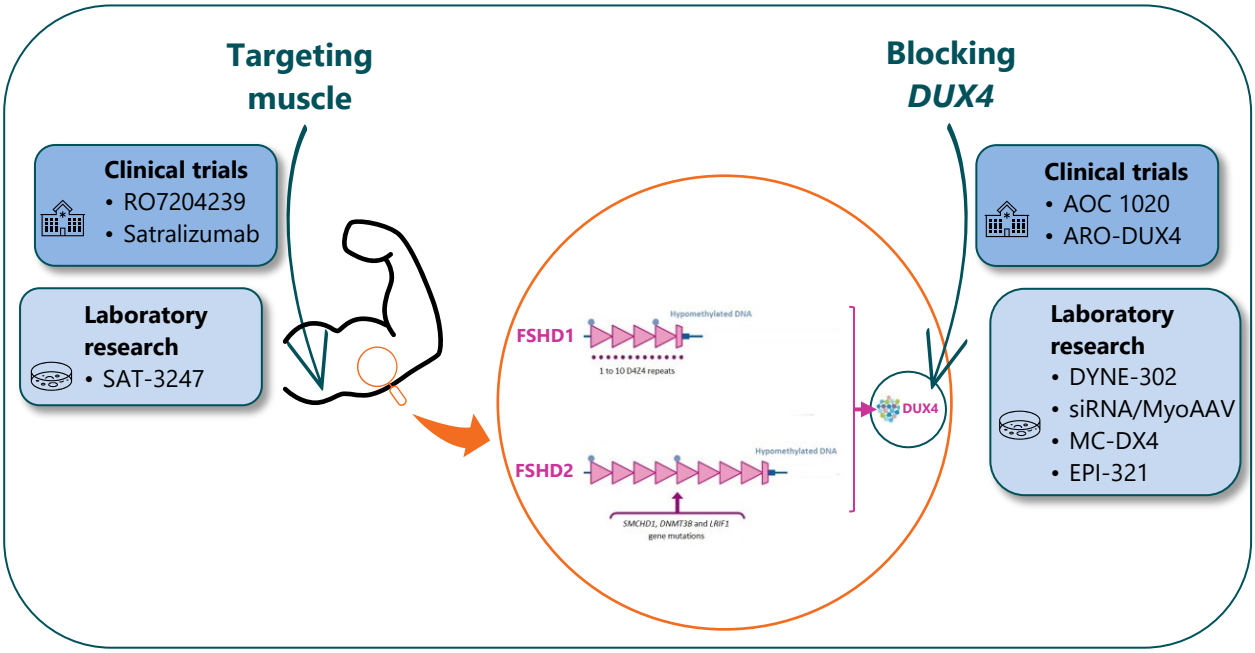


For more information on FSHD, please visit:
www.afm-telethon.fr/fr/fiches-maladies/myopathie-facio-scapulo-humerale [page in French]
https://www.afm-telethon.fr/fr/reperes: "Ma Maladie" ["My Disease"] reference document on FSHD [document in French]

Two main therapeutic approaches

Several drug candidates for FSHD are currently being evaluated with two main therapeutic goals:

- blocking *DUX4*,
- targeting muscle.



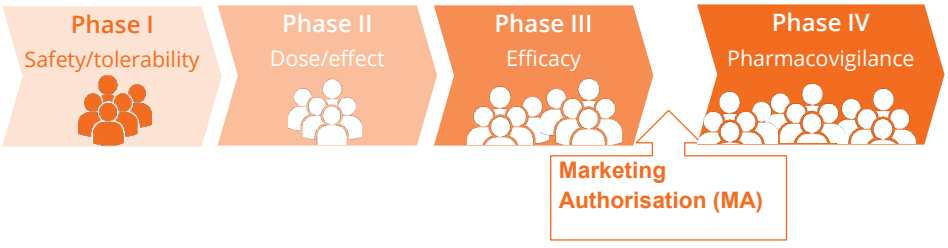
Clinical trials

Clinical trials consist of **assessing a potential treatment** (drug candidate, medical device...) in order to ensure that it is well tolerated and effective in treating a disease.

The product is tested during **successive phases (I, II, III, IV)** which each answer specific questions such as: is it well tolerated? What is the optimal dose? Is it effective and according to what criteria (walking ability, motor function, breathing...)?

After a product has received regulatory approval, it is then used in real life and continues to be monitored in order to refine knowledge and identify any unexpected or serious side effects that may occur.

https://www.afm-telethon.fr/fr/vivre-avec-la-maladie/mon-parcours-de-soins/les-essais-cliniques-en-pratique [page in French]



Suspension of losmapimod development

In September 2024, the pharmaceutical company Fulcrum Therapeutics announced that it was suspending development of its product, losmapimod.

This comes after the initial results were obtained from the REACH trial (a phase III trial) which evaluated losmapimod vs placebo in 260 adults with FSHD1 or FSHD2 over one year. The product did not increase the relative surface area that participants could reach with an outstretched arm (primary endpoint). The secondary endpoints were also not achieved.

Fulcrum Therapeutics. Press release 12 September 2024

A brief history of losmapimod in FSHD

- **In preclinical trials** carried out in cell and animal models of FSHD, losmapimod had been shown to reduce the expression of the *DUX4* gene by inhibiting an enzyme called p38 MAP kinase.
- In the **first phase I trial,** conducted in 20 FSHD1 patients and 10 healthy volunteers, the product was well tolerated.
- During the **phase II ReDUX4 trial,** conducted in 80 adults with FSHD1 over one year starting in August 2019, losmapimod had no effect on the expression of genes regulated by DUX4 in muscle (primary endpoint of the trial). However, disease progression over one year slowed down, and improved shoulder movement and less fat infiltration in certain muscles were observed.
- **The phase III, placebo-controlled REACH trial** was conducted in 260 adults with FSHD1 or FSHD2 over one year starting in July 2022, with two investigator sites in France (Nice and Paris). However, losmapimod did not achieve the primary endpoint of this trial.
- In September 2024, the pharmaceutical company Fulcrum Therapeutics announced that it was **suspending its development** of losmapimod.

- The important role of p38 MAP kinase (the enzyme which losmapimod inhibits) on the expression of the *DUX4* gene was highlighted during the early phase of muscle formation (myogenesis). However, it did not affect *DUX4* gene expression in the later phases of muscle development which may explain why losmapimod was unsuccessful when evaluated in adult populations.

Vangipurapu R. Sci Rep. 2024.

AOC 1020 for silencing the *DUX4* gene

Developed by Avidity Biosciences, AOC 1020 is a small interfering RNA molecule which targets *DUX4* mRNA. In animal models, a single intravenous injection of AOC 1020 slowed the progression of muscle weakness.

An RNA-based drug candidate

AOC 1020 is a small interfering RNA (siRNA) molecule conjugated to an antibody which binds to a receptor found on the surface of muscle cells (the transferrin receptor TfR1) in order to help it enter them. AOC 1020 then binds specifically to a target RNA molecule (the RNA of the *DUX4* gene) to destroy it.

Messenger RNA (mRNA) *is a replica of a region of DNA corresponding to a gene, which serves as a template for the synthesis of a protein. It is composed of a nucleotide sequence which determines the protein's amino acid sequence, i.e., its composition and structure.*

*The **"orphan drug"** designation is applied to drug candidates (whose efficacy has not yet been demonstrated) in rare diseases, with the aim of facilitating the various stages of their development.*

- AOC 1020 has been granted orphan drug status for FSHD by the European and American health authorities, as well as "fast track" designation, a process which accelerates certain stages of a drug's development.

- A phase I/II, placebo-controlled trial (FORTITUDE) is currently taking place in the United States to study the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of AOC 1020 in **90 people with FSHD1 or FSHD2.**

Phase I
Safety/tolerability

Phase II
Dose/effect

FORTITUDE trial

Canada, United States, United Kingdom	90 (16 to 70 years old)	Not recruiting	April 2023 – April 2027 1 year of follow-up

NCT05747924

- According to the initial results announced by Avidity Biosciences, the product has been well tolerated. In addition, AOC 1020 seems to significantly reduce the expression of genes regulated by DUX4 and improve muscle strength.
Avidity Biosciences. Press release 27 February 2025

*An **open-label trial** is a clinical trial in which the doctors and participants know what treatment is being administered.*

- An open-label extension of this trial called FORTITUDE-OLE started in July 2024 to evaluate the long-term effects of AOC 1020.

Phase I
Safety/tolerability

Phase II
Dose/effect

FORTITUDE-OLE extension study

Canada, United States, United Kingdom	84 (16 to 70 years old)	Recruiting	July 2024 – April 2028 4 years of follow-up

NCT06547216

ARO-DUX4 for blocking *DUX4*

The RNA interference drug candidate ARO-DUX4 was also designed to inhibit the *DUX4* gene. In mouse models of FSHD, treatment with ARO-DUX4 reduced *DUX4* mRNA and DUX4 target gene expression. Their weight, muscle atrophy and muscle function also improved.

- A trial sponsored by Arrowhead Pharmaceuticals which started in February 2024 is currently taking place to evaluate the effects of ARO-DUX4 in **60 adults with FSHD1.** In the first part of the trial, the participants receive either a single dose of the product or a placebo. In the second part, they receive two or four doses of the product (or a placebo).

Phase I
Safety/tolerability

ARO-DUX4 trial

Australia, New Zealand, Thailand	60 (18 to 70 years old)	Recruiting	Feb 2024 – Sept 2025 1 year of follow-up

NCT06131983

▪ A collaboration between Arrowhead Pharmaceuticals and Sarepta Therapeutics was announced in November 2024. It includes several therapeutic programmes developed by Arrowhead, such as the development of ARO-DUX4 in FSHD.
Sarepta Therapeutics. Press release 26 November 2024

RO7204239 for counteracting myostatin

RO7204239 is a drug candidate developed by the pharmaceutical company Hoffmann-La Roche to inhibit myostatin.

An anti-myostatin antibody
RO7204239 is an antibody that blocks myostatin (a natural inhibitor of muscle growth) with the aim of increasing muscle mass.

A phase II trial (MANOEUVRE) is evaluating its effects on the muscle volume of quadriceps muscles (thighs) in **48 ambulatory adults with FSHD1 or FSHD2.**

MANOEUVRE trial

Phase II
Dose/effect

Denmark, United States, Italy, United Kingdom	48 (18 to 65 years old)	Not recruiting	Feb 2023 – Oct 2026 2 years of follow-up

NCT05548556

Satralizumab for reducing inflammation

An initial study conducted on blood samples from 100 adults with FSHD1 revealed chronic inflammation, with an increase in levels of inflammatory cytokines and a decrease in levels of anti-inflammatory cytokines. Amongst these cytokines was interleukin-6 (IL-6), a potential biomarker of the disease's activity.

A biological marker (or biomarker)
A biomarker is a measurable parameter that indicates whether a biological process is normal or pathological. Identifying new biomarkers for a disease is very important for monitoring the course of the disease and the efficacy of new treatments. These markers can be physiological (change in blood pressure, heart rate...) or molecular (change in the expression of a protein...).

▪ Drawing on these findings, CHU de Nice [Nice University Hospital] launched a new trial in January 2024 to evaluate the effects of satralizumab, an antibody which targets IL-6 to **reduce inflammation.**

REINFORCE trial

Phase II
Dose/effect

France and Canada	40 (18 to 65 years old)	Recruiting	Jan 2024 – Jan 2027 2 years of follow-up

NCT06222827

Antioxidants for reducing cellular stress

In July 2012, a team from CHU de Montpellier [Montpellier University Hospital] evidenced an increase in oxidative stress in FSHD as well as a correlation between this oxidative stress and muscle weakness in the quadriceps.

Oxidative stress

Oxidative stress is a situation in which a cell no longer controls the presence of excessive toxic molecules called free radicals which are mainly produced by cellular respiration.
Free radicals are produced in mitochondria by the transformation of the oxygen used by cells to function (cellular respiration). They are toxic as they oxidise other molecules and damage cells.

- The **first clinical trial** to evaluate the effects of a combination of antioxidants (vitamin C, vitamin E, zinc and selenium) vs placebo was conducted in 53 FSHD patients.

- After four months of treatment, a reduction in oxidative stress was observed. In addition, an improvement in quadriceps endurance and contraction strength was reported in the antioxidants group. However, no significant statistical difference was observed between the treatment group and the placebo group in the two-minute walk test.

- In 2024, results from 10 patients on antioxidants and 10 on placebo showed an improvement in muscle volume, quality and strength and a reduction in oxidative stress.
Wilson VD et al. Free Radic Biol Med. 2024

- A **second clinical trial,** an open-label study running for three years involving 189 FSHD patients, was conducted by the team in Montpellier. The data is currently being analysed.

Routine care in FSHD

France	189 (over 7 years old)	Analysis in progress	April 2015 – July 2024 3 years of follow-up

NCT02622438

SOLVE FSHD for collectively seeking a cure

The latest

SOLVE FSHD is an organisation that combines collaboration and innovation with the aim of advancing research and treatments in FSHD. Its mission is to **find a cure for FSHD by 2027.** The organisation funds various projects with the aim of slowing down muscle degeneration, and improving muscle strength and the quality of life of patients. Its partners include several pharmaceutical companies such as Epicrispr Biotechnologies and miRecule as well as hospitals like CHU de Nice.
www.solvefshd.com

Observational studies currently taking place in France

Observational studies allow researchers to gain a better understanding of a disease, identify better monitoring or diagnostic tools and evaluate the effect of a treatment over a somewhat long period of time.

▪ In order to be able to optimally evaluate new treatments in clinical trials, it is essential to have reliable outcome measures. Several observational studies are currently working on this.

The ReSolve study is assessing two outcome measures: a functional composite outcome measure for FSHD (FSHD-COM) and a non-invasive muscle exam (electrical impedance myography).

ReSolve study

Abroad (outside France)

320 (18 to 75 years old)

Recruiting

March 2018 – March 2027 2 years of follow-up

NCT03458832

The ReSolve study is being conducted in Germany, the United States, Italy, the Netherlands, the United Kingdom and France.

▪ **ReSolve_France** (the French part of the study) is sponsored by CHU de Nice and is also taking place in Lille and Paris (at the Institut de Myologie [Institute of Myology]).

ReSolve_France study

France

100 (18 to 75 years old)

Not recruiting

Sept 2019 – Sept 2025 2 years of follow-up

NCT04038138

▪ The **ADVANCED study** is also currently taking place at CHU de Nice to assess outcome measures adapted for non-ambulatory FSHD patients in order to prepare for future clinical trials.

ADVANCED study

France

30 (over 18 years old)

Recruiting

April 2023 – April 2027 2 years of follow-up

NCT05453461

▪ CHU de Dijon [Dijon University Hospital] launched the **WANTED study** in order to compare different walking tests to other measures such as the Motor Function Measure (MFM) and physical activity time measured by an actimeter. These measures could be easier to use for assessing patients. This study is being conducted in adults with FSHD who are able to walk for at least six minutes (including intermittently).

WANTED study

France

60 (over 18 years old)

Recruiting

April 2024 – Oct 2026 2.5 years of follow-up

NCT06600308

▪ The **PROGRESS-FSHD study** is examining the feasibility of remotely evaluating patients using a mobile phone app called "myFSHD". This app can be used at home and in hospital, and features questionnaires on fatigue, pain, physical activity, sleep and quality of life to be filled in by the participants. The follow-up of this study is taking place in Lille, Nice and Paris.

PROGRESS-FSHD study

France

70 (18 to 75 years old)

Not recruiting

May 2023 – March 2025 1 year of follow-up

NCT05812144

MRI *or* ***magnetic resonance imaging*** *is a medical imaging technique which can obtain cross-sectional or volumetric images of an organ or area of the human body. The exam involves lying on a bed which slides into a cylindrical machine made from a very powerful magnet. MRI scans are not painful. However, being in a confined space, the length of the scan, being on your own and the noise from the machine can be a little bit scary.*

➤➤ Diagnostic des maladies neuromusculaires [Diagnosis of neuromuscular diseases], Savoir & Comprendre references documents, AFM-Téléthon.

▪ In order to better understand the natural history of FSHD2 and to assess inflammatory serum biomarkers and outcome measures for its progression, the **INSIGHT FSHD2 study** is currently taking place, with the French part of the study being conducted in Paris, Marseille and Nice. No drug candidates are being evaluated, but several medical exams are being carried as part of the study (blood tests, muscle and function tests, muscle MRIs, lung function tests, self-administered questionnaires...).

INSIGHT FSHD2 study

France

50 (18 to 75 years old)

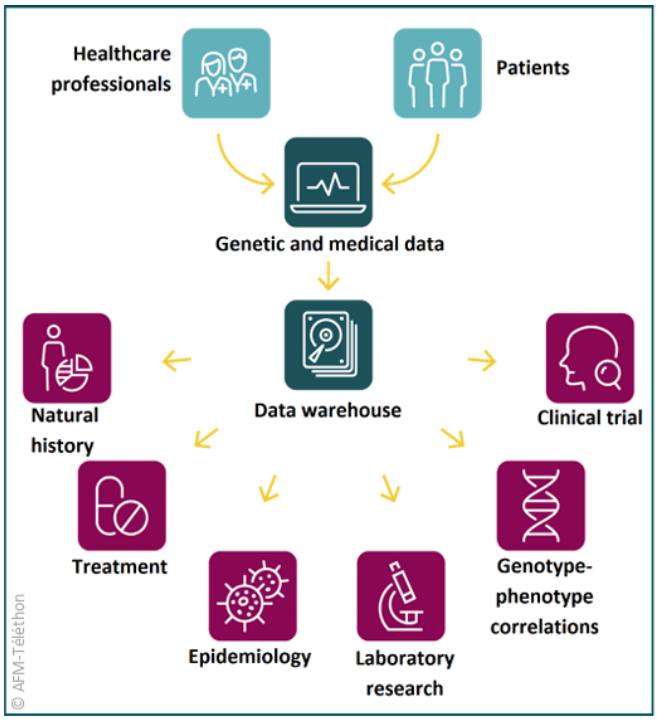
Recruiting

Oct 2023 – April 2026 1.5 years of follow-up

NCT06079567

Databases

Databases and registries collect medical and genetic data from people with the same disease.
Analysing this data helps to determine the natural history of the disease, establish genotype-phenotype correlations and recruit participants to clinical trials.



*The so-called **natural history** of a disease, as doctors refer to it, is the description of the different manifestations of a disease and their progression over time without treatment.*

***Genotype-phenotype correlation** studies look for links between genetic characteristics (genotype) and physical characteristics (phenotype, i.e. height, eye colour and shape, hair colour, disease manifestations....).
A connection can therefore be identified between the presence of a genetic mutation and the manifestations of a genetic disease.*

A French registry

▪ The Observatoire National Français des patients atteints de DMFSH [French National Registry for patients with FSHD] was created in June 2013. Funded by AFM-Téléthon, this data warehouse aims to gather genetic and clinical information from as many people as possible with FSHD in order to improve our understanding of the disease and accelerate the development of drugs.

▪ The genetic and clinical data in this registry comes from **self-administered questionnaires** filled in by patients and/or **clinical assessment forms** completed with their doctor during consultations.

The Observatoire National Français des patients atteints de DMFSH

France	1,308 patients in November 2024	Recruiting	Created in June 2013

Overview as of 31 March 2025

▪ The Observatoire contains data from **1,315 patients (1,274 patients with FSHD1 and 41 with FSHD2).**

Its goal is to collect data from 1,500 patients by 2027.

▪ A total of **41 centres** currently participate.

www.fshd.fr [page in French]

Registries outside of France

▪ Other countries such as the United Kingdom, the United States and China have also developed national FSHD registries.

▪ An American team analysed data from the American muscular dystrophy registry MD STARnet, with a particular focus on respiratory insufficiency in FSHD between 2008 and 2016. Only 20% of the 170 patients identified in the registry had undergone lung function tests. Amongst those tested and/or those who had been monitored for several years, respiratory insufficiency (generally mild) was frequently observed.

The researchers recommend that monitoring in FSHD patients should always include respiratory evaluation at diagnosis and at regular intervals as needed.

Mathews KD et al. Neuromuscul Disord. 2024

Other treatment avenues being studied

Various different treatment avenues are being evaluated in FSHD. Some target the molecular mechanisms involved in the disease (for example, expression of the *DUX4* gene or genes activated downstream) while others are focused on epigenetics or muscle structure. They are first tested in cell or animal models in preclinical trials.

Preclinical research - an essential step

Preclinical research involves studying the behaviour of drug candidates in cultured cells (*in vitro*) and animal models (*in vivo*). It also makes it possible to demonstrate the proof of concept of a product's action on the intended target so that it can then move on to clinical development. It is therefore an essential prerequisite for the administration of a drug candidate in humans. During the preclinical phase of developing a drug candidate, researchers study the pharmacology, pharmacokinetics and toxicology of the drug (mechanism of action, physical and chemical properties, pharmacokinetics and pharmacodynamics of the compound in the body, target organs, toxicity...). Preclinical research therefore makes it possible to determine an initial, non-toxic dose that can be administered to humans.
This data is essential when preparing a marketing authorisation (MA) application file for the future drug to be submitted to regulatory authorities.

Targeting *DUX4* gene expression

RNA-based therapies

These therapies use a small fragment of RNA (called interfering RNA such as microRNAs and siRNAs or antisense oligonucleotides in the form of RNA) which binds to a target mRNA molecule in order to destroy it or deactivate the production of the corresponding protein.
In FSHD, researchers use RNA-based strategies with the aim of inhibiting the production of the DUX4 protein.

DYNE-302

Developed by the pharmaceutical company Dyne Therapeutics, DYNE-302 is composed of a small interfering RNA (siRNA) molecule which binds to *DUX4* mRNA with the aim of reducing its expression. In order to help it enter muscle cells, this small RNA molecule is conjugated to an antibody which binds specifically to a receptor found on the surface of these muscle cells (the transferrin receptor TfR1), like the drug candidate AOC 1020 being evaluated in the FORTITUDE clinical trial.

▪ The initial results for DYNE-302 were presented in October 2024 at the 29th Annual Congress of the World Muscle Society. They showed that DYNE-302 significantly reduced the expression of *DUX4* in mouse models of the disease for at least three months. The structure and function of their muscles also improved.
Dyne Therapeutics. Press release 9 October 2024

An siRNA molecule transported by MyoAAV

The pharmaceutical company Kate Therapeutics is developing several RNA-based therapies in preclinical trials for the treatment of various neuromuscular diseases. For FSHD, they are developing a siRNA molecule transported by an adeno-associated virus (AAV) to silence *DUX4* mRNA in skeletal muscle (MyoAAV).

Adeno-associated viruses *(AAVs) are DNA viruses that can infect humans. However, they do not cause disease but instead trigger a mild immune response. Once inside a cell, the AAV expresses its genes (and those that have been introduced into its genome). They are used in genetic engineering as vectors for gene therapy.*

▪ In November 2024, the pharmaceutical company Novartis announced that it had acquired Kate Therapeutics and would continue to develop drug candidates in the various neuromuscular diseases concerned.
Novartis. Press release 21 November 2024

MC-DX4

In 2022, Sanofi announced its collaboration with miRecule, a pharmaceutical company which is developing an RNA-based therapy called MC-DX4 that targets *DUX4* mRNA.
▪ The two companies combined their technologies to create an RNA therapy coupled with an antibody that will allow it to reach muscle tissue more easily. This therapy is currently being studied in cell and animal models of the disease.
FSHD Society. News 31 December 2024

Targeting SIX transcription factors

American researchers identified regulators (transcription factors SIX1, 2 and 4) that promoted aberrant *DUX4* expression in muscle cells taken from FSHD1 and FSHD2 patients.
▪ Using small interfering RNAs to target SIX1, 2 and 4 (and *DUX4* mRNA indirectly) significantly reduced the expression of the *DUX4* gene and DUX4 target genes in cell models of the disease.
Fox A et al. Skelet Muscle. 2024

Modulating epigenetics

Epigenetics
Epigenetics is the study of non-genetic factors (food, medication, stress...) that can modify gene activation.
▪ Chromosome 4 typically has between 11 and 100 repeats in the D4Z4 region. In this region, DNA is methylated, meaning that it contains methyl groups that cause significant compaction and coiling of the DNA which affect gene expression in this location. These modifications to the structure of DNA are called epigenetic factors.
▪ In FSHD1 and FSHD2, DNA is less methylated (or hypomethylated) and chromatin is less compact and more open which leads to the anormal expression of the *DUX4* gene in muscle.
Targeting the methylation of the D4Z4 region is also being studied as a treatment avenue with the aim of blocking DUX4 expression.

EPI-321

In 2023, the drug candidate EPI-321 was granted orphan drug designation by the American health authorities. This product, developed by the pharmaceutical company Epicrispr Biotechnologies, is based on an approach derived from CRISPR technology which does not involve cutting DNA. It aims to restore the methylation of the D4Z4 region and suppress the expression of the *DUX4* gene. It is delivered to muscle by an AAV vector.
▪ In muscle cell models of FSHD, EPI-321 suppressed the expression of the *DUX4* gene and reduced muscle cell death.
▪ Epicrispr Biotechnologies recently announced that it had raised funds (with help from SOLVE FSHD) which should enable its first phase I clinical trial of EPI-321 in FSHD to be launched this year in New Zealand.
Epicrispr Biotechnologies. Press release 27 March 2025

*The **CRISPR/Cas9 system** enables changes to be made to the genome (a method known as genome editing). The principle consists of targeting a DNA sequence or gene in a cell in order to modify, repair or remove it.*

Promoting muscle regeneration

Muscle degeneration
In adults, FSHD causes the progressive weakening (degeneration) of muscle tissue.
In parallel with therapies focusing on the expression of the *DUX4* gene, other treatments are being developed to directly target muscle degeneration.

SAT-3247

The pharmaceutical company Satellos is developing a drug candidate called SAT-3247 which inhibits the AAK1 protein and, as a result, should regulate muscle regeneration independently of DUX4. When orally administered in mouse models of FSHD with muscle degeneration, it improved their muscle strength.

- Satellos recently launched a phase I trial involving this type of approach in another neuromuscular disease called Duchenne muscular dystrophy in order to regenerate skeletal muscle without directly targeting dystrophin (and therefore regardless of the *DMD* gene mutation status of patients).

Satellos. Press release 18 February 2025

Assessing more sensitive outcome measures for clinical trials

The number of clinical trials in FSHD is expected to continue to rise in the next few years with new drug candidates to evaluate. In order to prepare for this, taking into account the different symptoms and slow progression of the disease, it is important to identify homogeneous groups of patients and reliable and effective outcome measures.

A disease that usually progresses slowly

A natural history study of FSHD was conducted in the Netherlands over five years in 154 symptomatic patients with an average age of 51. They underwent several tests (Motor Function Measure, six-minute walk test...) upon their inclusion to the study and then again after five years.

- During these five years, **disease progression was minimal,** suggesting that the duration of clinical trials needs to be extended (the average duration is currently two years) and that more adapted and sensitive outcome measures need to be identified that can detect changes despite the slow progression of the disease.

Kools J et al. Muscle Nerve. 2025

A force test combining contraction speed and exercise duration in mice

By working with mouse models that reproduced a large number of FSHD characteristics, a collaboration involving two teams of researchers based in London and Chambery was able to develop a new force test capable of measuring the power of "moving" muscle. Unlike other muscle force tests performed without muscle movement, this test is able to better reflect and assess **the movements made in everyday life.** It has already provided a better understanding of muscle function in mice and could be used in humans, particularly in clinical trials.

Sohn S et al. Int J Mol Sci. 2024

Muscle in 3D

Laboratory researchers generally work with FSHD patient cell models grown in a single-layer (two-dimensional) culture or mice that reproduce certain characteristics of the disease.

▪ For the first time, **a three-dimensional tissue engineered skeletal muscle (3D-TESM) model** has been developed from FSHD1 patient stem cells.

Several physiological characteristics of the disease could be observed compared to healthy muscle such as *DUX4* gene and DUX4 target gene expression, thinner muscle fibres and muscle weakness.

This new model is more comprehensive than cell cultures and should be a good research tool for studying diseased muscle function and identifying potential treatments, with a particular focus on reducing *DUX4* gene expression.

Franken M et al. Brain. 2024

The role of the *SMCHD1* gene becomes clearer

▪ At the 21st Journées de la Société Française de Myologie (annual meeting held by the Société Française de Myologie [French Society of Myology]), an overview of FSHD was carried out by the researcher Frédérique Magdinier (Marseille). Her team is particularly interested in the *SMCHD1* gene which is mutated in 80% of FSHD2 patients and impacts chromatin relaxation.

F Magdinier (2024). JSFM 2024. Clermont-Ferrand, France [page in French]

▪ Another team highlighted a role of SMCHD1 which does not depend on DUX4 - it activates genes involved in the development of muscle precursor cells (myoblasts). As a result, *SMCHD1* gene mutations in FSHD2 lead to **a decrease in the number of myoblasts,** independent of DUX4, which can impair muscle regeneration.

Wong MM et al. Nucleic Acids Res. 2024

A focus on younger patients

Factors influencing the age of onset of the disease

▪ A large-scale study conducted in 874 FSHD1 patients (804 symptomatic and 70 asymptomatic) monitored at the Fujian Neuromedical Centre in China between 2001 and 2023 provided information on the age of onset of the disease. Several independent parameters such as **male sex, a low number of D4Z4 repeats, hypomethylation of the D4Z4 region, non-mosaic mutation** and **de novo mutation** (a mutation that occurs spontaneously and was not inherited from a parent) were associated with an early onset.

In addition, the earlier the onset of the disease, the higher the age-corrected clinical severity score will be and the earlier the onset of lower limb involvement will be.

Zheng F et al. Brain. 2025

An "early-onset" form

▪ A workshop organised by the European Neuromuscular Centre (ENMC) dedicated to the paediatric form of FSHD took place between 1 and 3 November 2024 in Hoofddorp (Netherlands). It brought together 27 participants (clinicians, researchers, associations) from 14 different countries.

At the event, a consensus was reached that "infantile forms" should now be referred to as the **"early-onset form"**, with FSHD being considered as a single disease with a very variable age of onset (from childhood to old age). The workshop also focused on developing clinical management guidelines for this early-onset form.
279th ENMC International Workshop. ENMC.

Other clinical study results

French guidelines for FSHD published internationally

▪ At the end of 2021, experts from FILNEMUS (a French rare diseases healthcare network) specialist centres in France published a PNDS (Protocole National de Diagnostic et de Soins [French National Diagnosis and Care Protocol]) for FSHD for healthcare professionals.
HAS, December 2021 [document in French]

Protocoles Nationaux de Diagnostic et de Soins
The objective of PNDSs is to provide explicit instructions to healthcare professionals regarding optimal treatment and management and care pathways for patients with a specific rare disease. As a result, they help optimise and harmonise the care and follow-up of rare diseases throughout France.
Together with a scientific argument and a summary for family doctors, all PNDSs are available on the HAS (Haute Autorité de Santé [French National Authority for Health]) website.
www.has-sante.fr/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds [page in French]

▪ These authors also published an article in the Journal of Neurology in July 2024 which outlined the main points of the PNDS, including the (sometimes atypical) signs of FSHD, the optimal approach to making a diagnosis (primarily based on symptoms and genetic testing), and the importance of regular monitoring (every six months for children and every one to two years for adults) and multidisciplinary care coordinated by specialist centres and rehabilitative care facilities.
Attarian S et al. J Neurol. 2024

The benefits of exercise at muscle fibre level

As part of a French/Swedish study lasting nearly six months, eight adults with FSHD1 followed a tailored exercise programme at home which consisted of completing a 35-minute session on a stationary bike three times a week. Eight other adults with FSHD1 were instructed not to change their usual activities.
▪ The adapted exercise training induced an **increase in the size of muscle fibres** affected by FSHD. It also brought about an **increase in the number of satellite cells** (muscle stem cells that enable muscle tissue to regenerate) in a certain type of muscle fibre, all without exacerbating the disease or impairing muscle regenerative capacity. These results support the recommendation that adapted exercise should be practised on a regular basis by patients with FSHD.
Horwath O et al. J Physiol. 2025

When FSHD masks another disease

A frequent association with inflammatory myopathy

By analysing data from 1,750 people with inflammatory myopathy monitored in a French or Italian neuromuscular disease centre between 2012 and 2024, clinicians identified **five people who had both FSHD and inflammatory myopathy.** Two had FSHD and then developed inflammatory myopathy later, two had inflammatory myopathy and then were diagnosed with FSHD, and one was diagnosed with both diseases at the same time.

- The clinicians suggest considering inflammatory myopathy in FSHD patients who experience rapid clinical worsening. By contrast, they also suggest ruling out FSHD in inflammatory myopathy patients who have atypical symptoms and a disease that progresses slowly.

Lauletta A et al. J Neurol Sci. 2025.

Possible association with other neuromuscular diseases

Researchers from Nice, in collaboration with several other European teams, analysed clinical and genetic data from 157 FSHD1 patients. The vast majority had the classic features of the disease. However, 27 displayed atypical features. In 14 of them, **another neurological disorder was identified** including myotonic dystrophy (type 1 and 2), limb-girdle muscular dystrophy (calpainopathy), mitochondrial myopathy and Huntington's disease. That said, further investigations will be necessary in order to determine whether these comorbidities are coincidental or not.

Puma A et al. Eur J Hum Genet. 2025

The latest

The first **FSHD Connect Europe** meeting will take place in Amsterdam (Netherlands) from 13 to 15 June 2025. Organised by FSHD Europe in collaboration with the FSHD Society, this event will bring together FSHD patients, their families, clinicians and researchers for the first time in Europe, allowing them to connect and share their experiences.

fshd-connecteurope.eu

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Keep up to date with FSHD research news throughout the year on the AFM-Téléthon website:

www.afm-telethon.fr/en