JUNE 2024

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2024 in myotonic dystrophy type 1

© Jean-Yves Seguy/ AFM-Téléthon

This document, published to coincide with the AFM-Téléthon General Meeting 2024, presents myotonic dystrophy type 1 research news from the past year (ongoing studies and clinical trials, scientific and medical publications, etc.).

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

Table of contents

Written by
- Magali Bichat - Myoinfo, Neuromuscular Disease Information Department, AFM-Téléthon, Évry

Verified by
- Alain Geille from the AFM-Téléthon Groupe d'Intérêt Steinert (DM1 & DM2) [DM1 and DM2 Special Interest Group], Évry
- Geneviève Gourdon Centre de Recherche en Myologie [Myology Research Centre], Institut de Myologie [Institute of Myology], Hôpital Pitié-Salpêtrière [Pitié-Salpêtrière Hospital], Paris
- Nathalie Loux Directorate of Scientific Operations and Innovation at AFM-Téléthon, Évry
- Sabrina Sayah Neuromyology Department, Institut de Myologie and Hôpital Pitié-Salpêtrière, Paris

Translated by
Emily Scott

*
* *

4 Highlights from the past 12 months

The rise of RNA-based drugs

11 drug candidates in trials, including **6** RNA-based drug candidates.

Del-desiran
ATX-01 DYNE-
PGN-EDODM1 101
ARO-DM1 VX-670

Drugs using this technology have already been approved to treat other rare diseases (SMA and transthyretin amyloidosis).

Dynamic clinical research presented at conferences

- The 14th International Myotonic Dystrophy Consortium Meeting (**IDMC-14**) was held in April 2024 in the Netherlands, with the support of AFM-Téléthon, together with the 4th edition of the **Euro-DyMA Pharma's Day.**
- **7** presentations on drug candidates being trialled in humans and the benefits of cardiac and respiratory care on the life expectancy of patients.

Trait d'Union newsletter number 21 – May 2024

- **Information on clinical trials** at other conferences: Myology 2024, the American Academy of Neurology (AAN) Annual Meeting, the American Society of Gene & Cell Therapy (ASGCT) Annual Meeting, the MDA Clinical and Scientific Conference, etc.

A closer look at Euro-DyMA

12 European patient organisations committed to the fight against DM1 and DM2.

EURO-DYMA Myotonic Dystrophies

→ harmonising good practices and knowledge of these diseases in the European Union.
→ giving patients a voice in clinical trials and studies being conducted or planned in Europe.

2-3 May 2025

Pharma's Day

Organised by Euro-DyMA and the Myotonic Dystrophy Foundation

Myotonic dystrophy type 1 DM1

This disease, which is also known as Steinert's disease, mainly affects the muscles but can also impact other organs to a greater or lesser extent.

Common symptoms

- DM1 is a **"multisystem" disorder,** meaning it affects several different organs (muscles, the heart, the respiratory system, the digestive system, the endocrine system and the nervous
- Muscles decrease in volume, become weak (**dystrophy**) and have difficulty relaxing after they contract (**myotonia**).
- Symptoms **vary greatly** from patient to patient, with some forms remaining asymptomatic (no symptoms) until old age while others are very severe and start at birth.

Five forms classified according to age of onset of first symptoms

Congenital-onset	Childhood-onset	Juvenile-onset	Adult-onset (classic)	Late-onset
From birth	Before the age of 10	Before the age of 20	Before the age of 40	After the age of 40

Adult-onset DM1 is the most common form, with the first signs of muscle impairment occurring during adulthood (muscle stiffness, walking difficulties, increasing fatigue, etc.)

Management and treatment

- ☑ **Multidisciplinary treatment** of symptoms at specialist centres.
- ☑ Preventing complications.
- ☑ Improving quality of life.

In numbers

10 to 50 people in every 100,000 have DM1

5,000 to 8,000 patients in France

Over 200 scientific articles published between May 2023 and May 2024 *(PubMed)*

What causes it?

☑ DM1 is caused by a mutation in the ***DMPK*** (dystrophia myotonica protein kinase) **gene** on chromosome 19. This type of mutation is called a repeat expansion and involves a segment of DNA in a gene being repeated more than usual. In DM1, this segment contains three nucleotides and is written as **CTG** (cytosine, thymine and guanine).

Person without DM1
5 to 37 CTG repeats

Person with DM1
50 to several thousand CTG repeats

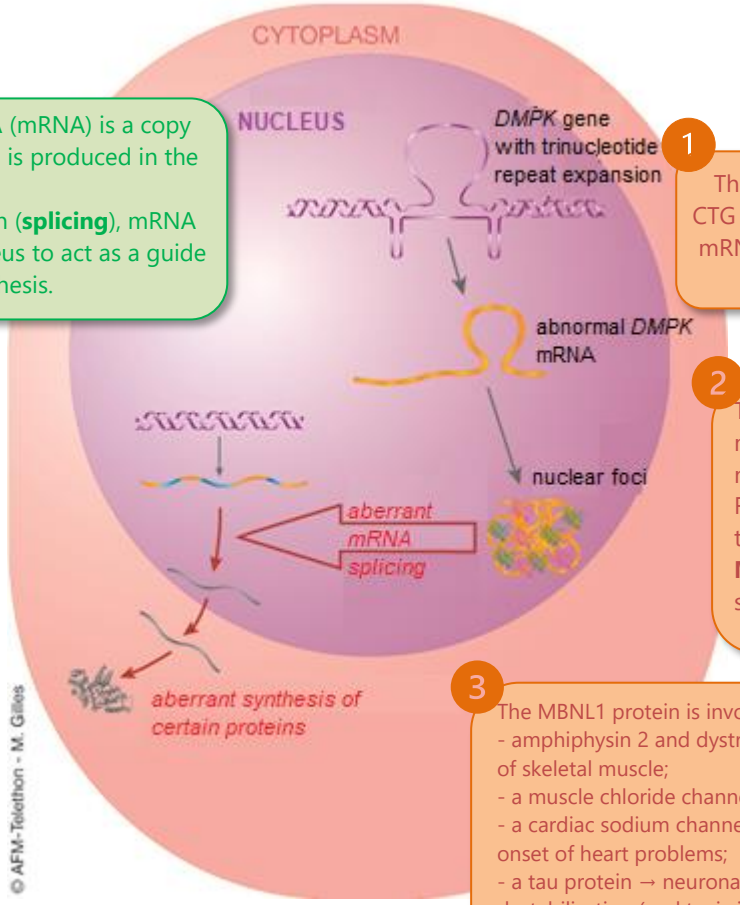
How is it inherited?

☑ **Autosomal dominant** inheritance: only one copy of the mutated *DMPK* gene needs to be inherited for myotonic dystrophy type 1 to develop.

☑ **Genetic anticipation**: when passed from one generation to the next, the number of CTG repeats increases and can make symptoms more severe or appear at an earlier age.

From genetic mutation to symptoms

Messenger RNA (mRNA) is a copy of a gene which is produced in the nucleus.
After maturation (**splicing**), mRNA leaves the nucleus to act as a guide for protein synthesis.



1 The abnormally high number of CTG repeats is reproduced in *DMPK* mRNA, causing these molecules to have abnormal structures.

2 The mutated *DMPK* mRNA molecules accumulate in the nucleus and form foci in which RNA-binding proteins become trapped. These proteins, such as **MBNL1** and **CUGBP1**, regulate the splicing of mRNA in cells.

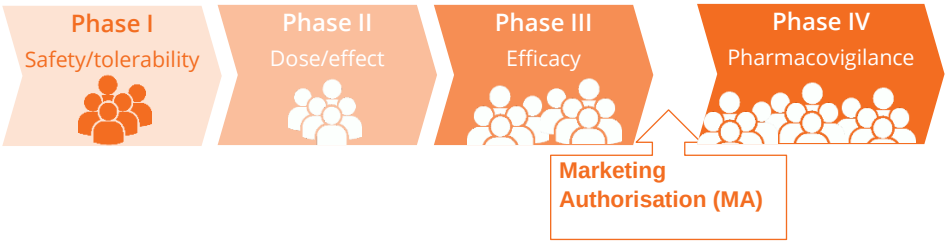
3 The MBNL1 protein is involved in the regulation of:
- amphiphysin 2 and dystrophin → gradual weakening of skeletal muscle;
- a muscle chloride channel → myotonia;
- a cardiac sodium channel and cardiac troponin → onset of heart problems;
- a tau protein → neuronal cytoskeleton destabilisation (and toxic in Alzheimer's disease);
- an insulin receptor → insulin resistance.

For more information on DM1, please visit:
www.afm-telethon.fr/fr/fiches-maladies/maladie-de-steinert [page in French]

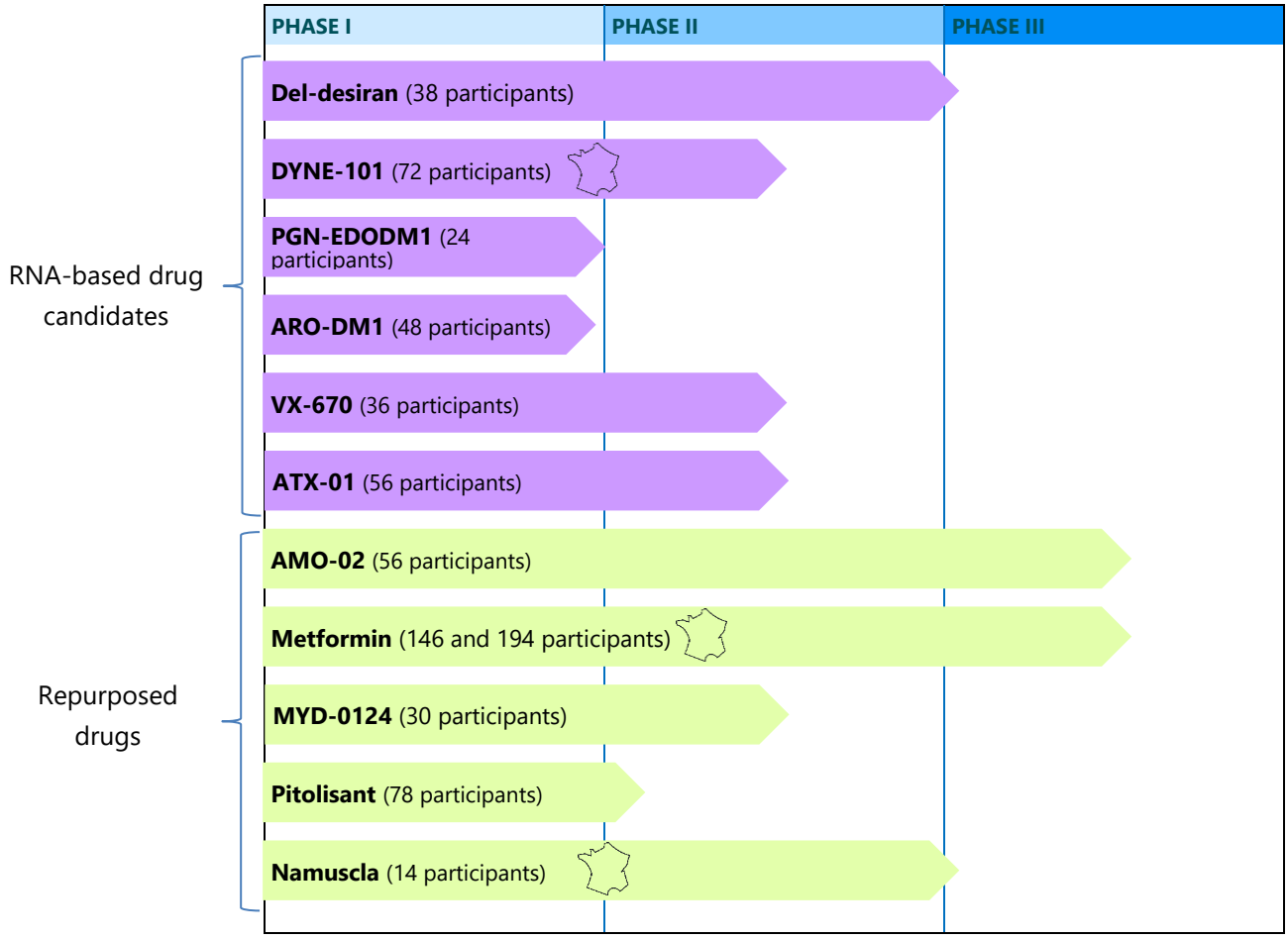
Clinical trials

Clinical trials consist of assessing a potential treatment (drug candidate, medical device, etc.) 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, etc.)? After marketing, the product 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.

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



▪ In June 2024, 11 drug candidates were undergoing trials in myotonic dystrophy type 1 (DM1). These drug candidates were either RNA-based drugs developed specifically to target the mutations that cause DM1, or existing drugs which have previously been approved to treat other diseases that are being reevaluated in DM1 (drug repurposing).



RNA-based drug candidates
Several pharmaceutical companies have synthesised small fragments of RNA capable of binding specifically to *DMPK* mRNA molecules and causing them to break down.
Researchers categorise them into different types (antisense oligonucleotides, small interfering RNAs (siRNAs), microRNAs, etc.) depending on their size and chemical makeup and they have been optimised to enable them to penetrate muscle cells more effectively.
Del-desiran and DYNE-101 are conjugated to a fragment antibody that binds to TfR1 (a muscle cell surface receptor) while PGN-EDODM1 and VX-670 are conjugated to a peptide which is able to cross the cell membrane.

Del-desiran (AOC 1001) – MARINA and HARBOR trials

Developed by Avidity Biosciences, del-desiran (AOC 1001 or delpacibart etedesiran) is a small interfering RNA (siRNA) designed to address the abnormally high number of CTG repeats present in *DMPK* mRNA. A trial is currently taking place in the United States. New data shared by the pharmaceutical company in March 2024 seemed very encouraging and showed long-lasting improvements in myotonia and muscle strength in myotonic dystrophy type 1.

▪ Initial trials in cell and animal models of DM1 enabled del-desiran to be granted orphan drug designation by the European and American health authorities in order to facilitate its clinical development.
In light of the preliminary results of the clinical trials, the United States Food and Drug Administration (FDA) also granted del-desiran breakthrough therapy designation (the company's lead clinical development programme) in May 2024 in order to accelerate its development.
Avidity Biosciences. Press release 8 May 2024

*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.*

▪ The MARINA trial was conducted in the United States in order to evaluate the safety and tolerability of del-desiran in 37 DM1 patients. The drug candidate was tested against a placebo for six months.
The results of this first phase were presented at the American Academy of Neurology Annual Meeting in April 2023.
- In every participant that received AOC 1001, the *DMPK* reduction observed in muscle (45% on average) led to a mild improvement in splicing abnormalities characteristic of DM1.
- Myotonia in the hands was reduced (as early as six weeks after treatment for some participants).
- Their muscle strength improved compared to those on the placebo.
- Any side effects experienced were mild in the majority of participants.

Johnson NE et al. AAN scientific abstracts – April 2023

▪ This first step was followed by an open-label extension during which all the participants received del-desiran for a further six months. Results after a year announced at the Muscular Dystrophy Association Clinical & Scientific Conference in March 2024 showed continued improvements in muscle strength and myotonia during this period. All of the participants were more active in their daily lives than they were at the start of the trial.
Johnson N et al. MDA Clinical & Scientific Conference 2024

Phase II
Dose/effect

MARINA-OLE trial

United States | **37 (18 to 66 years old)** | **Active** (not recruiting) | **Aug 2022 – June 2025 2 years of follow-up**

NCT05479981

▪ Encouraged by these results, in June 2024, Avidity Biosciences launched a new phase III clinical trial (the HARBOR trial) in order to test del-desiran in a larger number of patients.

Phase III
Efficacy

HARBOR trial

Abroad (outside France) | **150 (18 to 65 years old)** | **Recruiting** | **May 2024 – April 2027 1 year of follow-up**

NCT06411288

DYNE-101 – ACHIEVE trial

DYNE-101 is an optimised antisense oligonucleotide developed by Dyne Therapeutics. It is a small fragment of RNA that targets mRNA from the mutated *DMPK* gene and causes it to break down. An international trial is currently underway, the initial analysis of which showed positive signs regarding its efficacy.

▪ The ACHIEVE trial is evaluating DYNE-101 in patients for the first time after encouraging results were obtained from animal models of myotonic dystrophy type 1. Its objectives are to assess the safety of DYNE-101, determine the dose and frequency of administration that will be recommended for future trials and look for evidence of its activity in muscle cells against a placebo.
Its protocol was a collaborative effort which involved patient organisations with the aim of reducing the fatigue and constraints caused by participation in a clinical trial.
Furlong P et al. Res Involv Engagem. 2024

▪ In May 2023, the drug candidate was granted orphan drug designation by the European Medicines Agency (EMA) in order to facilitate its continued development.
Dyne Therapeutics. Press release 25 May 2023

Phase I
Safety/tolerability

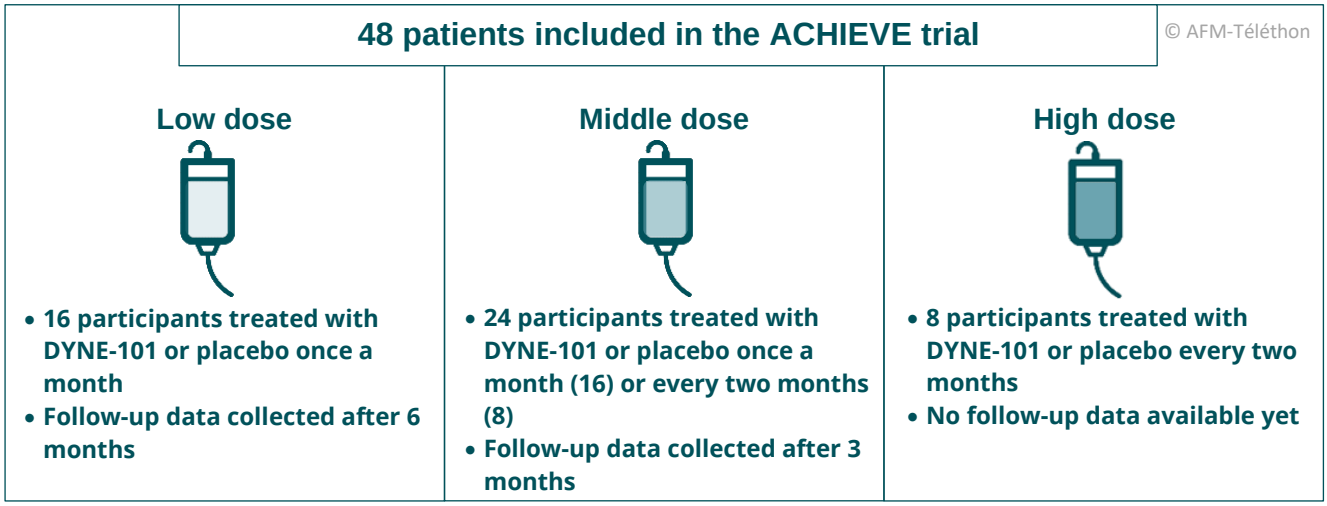
Phase II
Dose/effect

ACHIEVE trial

France and abroad | **72 (18 to 49 years old)** | **Recruiting** | **Sept 2022 – July 2026 6 months of follow-up**

NCT05481879

In a press release in January 2024, Dyne Therapeutics announced the preliminary results of the trial. These results involved 48 participants divided into three groups who received escalating doses of the product or a placebo.



➔ The treatment seems to be well tolerated at the three doses evaluated. No serious side effects have been reported so far.
➔ Laboratory tests showed that DYNE-101 had an impact on muscle cells (reduced amount of toxic *DMPK* RNA and altered splicing caused by mutated *DMPK* RNA) in the first two cohorts who were treated with low and intermediate doses.

For the first group, who were treated with the low dose, the data collected after six months indicated that:
➔ the participants took almost four seconds less on average to unclench their closed fists, a movement that is made slower by myotonia;
➔ Myotonic Dystrophy Health Index (MDHI) scores were better. This DM1-specific questionnaire uses 17 subscales (inability to carry out activities, pain, vision problems, etc.) to measure disease burden. Improvements were seen, particularly in terms of fatigue.
Dyne Therapeutics. Press release 3 January 2024

▪ A second press release published in May 2024 confirmed these positive trends both in terms of the safety and tolerability of the product (with a fourth dose currently being evaluated) and its effects on myotonia, muscle strength and quality of everyday life. The ACHIEVE trial is still underway.
Dyne Therapeutics. Press release 20 May 2024

PGN-EDODM1 – FREEDOM-DM1 trial

PGN-EDODM1 is an optimised antisense oligonucleotide developed by PepGen. It was designed to be able to penetrate all types of muscle cells (skeletal, smooth and cardiac) and target CUG repeats in mutated *DMPK* RNA and therefore prevent MBNL1 protein binding.
Preclinical studies have shown that the drug candidate is well tolerated and seems to be effective in various models of the disease.

Skeletal muscles *are muscles that are attached to bones. They are under voluntary control and move different parts of the body by contracting.*
Smooth muscle *is found in the walls of blood vessels, the digestive tract, the urinary tract and some organs. This type of muscle contracts involuntarily. Its organisation is different to that of skeletal muscle.*

▪ A North American, placebo-controlled, dose-escalation trial is evaluating the safety and tolerability of single injections of PGN-EDODM1 in a small number of adults with DM1.
Recruitment started in the United States and Canada in December 2023.

Phase I
Safety/tolerability

FREEDOM-DM1 trial

Abroad (outside France)	24 (18 to 50 years old)	Recruiting	Dec 2023 – April 2025 4 months of follow-up

NCT06204809

ARO-DM1

ARO-DM1 is a peptide-conjugated siRNA designed to silence *DMPK* mRNA in muscle cells. This effect was confirmed in preclinical studies, the results of which were presented at the Muscular Dystrophy Association Clinical & Scientific Conference in March 2024. This drug candidate was developed by Arrowhead Pharmaceuticals.
Van Dyke J et al. 2024 Muscular Dystrophy Association Clinical & Scientific Conference

▪ A placebo-controlled, dose-escalation trial is currently evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple injections of the product. The trial is being conducted in Australia and New Zealand and the first participants were included in March 2024.

Phase I
Safety/tolerability

ARO-DM1 trial

Abroad (outside France)	48 (18 to 65 years old)	Recruiting	March 2024 – Oct 2026 1 year of follow-up

NCT06138743

VX-670 – Galileo trial

VX-670 is an oligonucleotide developed by Vertex Pharmaceuticals Incorporated. It is linked to a cyclic peptide to improve its penetration into cells.

▪ A placebo-controlled trial is currently evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of VX-670 over two stages. The first involves a single injection where the dose gradually increases from participant to participant, while the second involves multiple injections (depending on the data obtained during the previous stage).
Recruitment began in Canada and Australia in February 2024.

Phase I
Safety/tolerability

Phase II
Dose/effect

Galileo trial

Abroad (outside France)	36 (18 to 64 years old)	Recruiting	Feb 2024 – Dec 2026 6 months of follow-up

NCT06185764

ATX-01- ArthemiR trial

Developed by ARTHEx Biotech, ATX-01 is an antimiR (synthetic single stranded oligonucleotide). It inhibits a natural microRNA called miR-23b which regulates MBNL1 protein synthesis. According to preclinical trials, the product has an effect on both the MBNL protein (whose levels increased) and toxic *DMPK* mRNA (which was reduced).
ATX-01 has been granted orphan drug designation in the United States and Europe.
ARTHEx Biotech. Press release 19 April 2024

MicroRNAs (miRNAs)
MicroRNAs are small RNA molecules which are able to regulate the production of a given protein by binding specifically to its messenger RNA. They are involved in the control of many biological processes.
They are also currently being studied as potential therapeutic targets. Targeting microRNAs that are specifically deregulated in DM1 could make it possible to compensate for certain disturbances linked to the disease.

▪ A clinical trial was launched to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ATX-01, and to determine the best dose to administer.

ArthemiR trial

Abroad (outside France)

56 (18 to 64 years old)

Recruiting

May 2024 – Dec 2025
4 months of follow-up

NCT06300307

Phase I
Safety/tolerability

Phase II
Dose/effect

AMO-02 – REACH CDM trial

AMO-02 (tideglusib) is a drug candidate developed by AMO Pharma. It was granted orphan drug designation in the United States in 2017. In 2020, the results from an initial clinical assessment of 16 DM1 patients treated for three months showed improvements in cognitive performance as well as a decrease in fatigue and behavioural problems. A new trial in around 50 children with the congenital-onset form of DM1 obtained mixed results.

Inhibiting the GSK3β enzyme
In DM1, DMPK gene mutations disrupt the activity of several molecules, including that of the GSK3β enzyme which is increased in certain tissues. This increase in activity impairs the formation of nerve and muscle tissue.
AMO-02 is a GSK3β enzyme inhibitor. GSK3β inhibition normalises the activity of CUGBP1, a regulatory protein that is overexpressed in DM1. This improves general cell function. AMO-02 corrects cell abnormalities in animal models of DM1 and improves muscle strength in mice whether treated very early or during adulthood.
Lutz M et al. Int J Mol Sci. 2023

*An **enzyme** is a protein that specifically allows, facilitates or accelerates a particular chemical reaction in our bodies (cell digestion, protein synthesis, DNA replication, etc.).*

▪ During the REACH CDM trial, 56 children and adolescents with the congenital-onset form of DM1 received either AMO-02 or a placebo for six months. The results were announced by press release in September 2023.

The primary endpoint was the scores obtained on the "Clinician-Completed Congenital DM1 Rating Scale", a clinical questionnaire completed by a doctor which is used to measure the general impact of the congenital-onset form of DM1. The scores did not show any differences between the patients who received AMO-02 and those who took the placebo (clinical benefits were seen in both groups).

However, AMO Pharma announced that significant improvements were measured with regards to physical (10-metre walk test) and cognitive (vocabulary test) abilities as well as reduced levels of creatine kinase (an enzyme that indicates muscle and cardiac damage) in the patients treated with AMO-02.

AMO Pharma. Press release 6 September 2023

The placebo effect in clinical trials

The act of taking part in a clinical trial alone can have a beneficial effect on a patient's symptoms. This is called the placebo effect. In order to obtain reliable clinical trial results, a drug candidate is often compared to a drug that looks identical to the drug candidate but is pharmacologically inactive - the placebo. The placebo effect is very real and has itself become a subject of study, enabling medical practices in both clinical trials and the daily monitoring of patients to improve.

- The trial has been extended with an open-label phase during which all participants will receive the treatment.

Phase II
Dose/effect

Phase III
Efficacy

Extension of the REACH CDM trial

Abroad (outside France)	76 (6 to 45 years old)	Recruiting	Aug 2021 – March 2025 Up to 2.5 years of follow-up

NCT05004129

AMO Pharma also announced its intension to conduct a phase III trial in adults with the adult-onset form of the disease in order to continue the development of its drug candidate.

AMO Pharma. Press release 2 May 2024.

Metformin

Metformin is a drug used to treat type 2 diabetes. Its potential anticancer, cardioprotective and neuroprotective properties (in Alzheimer's disease, depression, etc.) and ability to fight the effects of aging and obesity are currently being studied. Following research conducted by the I-Stem laboratory, the first clinical trial in DM1 was carried out in France, with the support of AFM-Téléthon, which showed its therapeutic potential in the disease. A new phase III trial (METFORMYO) is currently preparing to start recruiting participants in France.

I-Stem *is a research centre supported by AFM-Téléthon which works with stem cells to study and treat monogenic diseases.*
I-Stem works on cell therapy in order to restore function to tissue and organs using stem cell transplants, and tools developed from stem cells in order to better understand the mechanisms at play in rare diseases and discover new drugs.
www.istem.eu

Years' worth of research on metformin in DM1

2015: laboratory research	2018: first clinical trial in 40 patients	2019: study of over 900 DM1 patient records
• Correction of splicing defects in cells from DM1 patients.	• Improvement in walking ability • No changes in other parameters (myotonia, muscle strength, etc.)	• Seemed to reduce the risk of cancer in DM1 patients and diabetics.

A mechanism of action to be clarified

Metformin has many targets within cells. Researchers reviewed the mechanisms which may be able to explain its potential beneficial effects in neuromuscular diseases:
-reducing inflammation (a reaction that enables the body to protect itself from attack such as when cells are damaged),
-controlling autophagy (a process which recycles damaged cells),
-regulating mitochondria (which provide energy for cells to use).
There are many ways to understand how the drug works and how to get the most out of it.

Shang R et al. Front Neurol. 2023

*The **FILNEMUS rare neuromuscular diseases healthcare network** facilitates, coordinates and encourages interactions between those involved in the diagnosis, treatment and study of neuromuscular diseases (specialist centres, diagnostic laboratories, research teams, patient organisations, etc.). It was created in February 2014 as part of the second French National Plan for Rare Diseases 2011-2014.*

www.filnemus.fr [website in French]

Two trials in Europe

▪ The METFORMYO trial, supported by the AP-HP [Greater Paris University Hospitals], is currently being coordinated by Prof. Pascal Laforêt at the Hôpital Raymond-Poincaré [Raymond-Poincaré Hospital] in Garches. Recruitment will mainly be aimed at patients who are being monitored at FILNEMUS specialist centres.

METFORMYO trial

Phase III
Efficacy

France	142 (18 to 70 years old)	Not yet recruiting	March 2024 – Oct 2026 1 year of follow-up

NCT05532813

▪ Another metformin trial, which involved just under 200 DM1 patients, was conducted by the Neurosciences Department at the University of Rome Tor Vergata (Italy).

MetMyd trial

Phase III
Efficacy

Italy	194 (18 to 64 years old)	Analysis in progress	Launched in Jan 2020 2 years of follow-up

EudraCT number 2018-000692-32

MYD-0124

MYD-0124 is a well-established antibiotic (erythromycin) that has been shown to have beneficial effects on myotonia in mice with DM1. This small molecule is able to bind to CUG repeats in mutated *DMPK* RNA. This in turn brings about the release of MBNL regulatory proteins and the correction of splicing abnormalities in mRNA targeted by MBNL proteins.

- A phase II clinical trial conducted in 30 patients in Japan showed that treatment for six months was well tolerated and corrected certain splicing abnormalities that are characteristic of cells from DM1 patients, reflecting the potential efficacy of this drug.

A new phase III trial will be needed to confirm this.

Nakamori M et al. EClinicalMedicine. 2023

Pitolisant

Pitolisant (Wakix®) is a drug used to treat narcolepsy. A study showed that it also reduces daytime sleepiness in this disease.

The pharmaceutical company Harmony Biosciences evaluated its efficacy in myotonic dystrophy type 1. The preliminary results were presented at SLEEP 2024, a conference dedicated to sleep research. After three months of treatment, the participants who took pitolisant were less tired and less sleepy than those who received the placebo.

Harmony Biosciences is therefore now planning a phase III trial to confirm these results in a larger number of patients using a new formulation of the drug candidate.

Seiden D et al. – poster LBA 1278 annual meeting of the Associated Professional Sleep Societies, "SLEEP 2024"

Phase II
Dose/effect

Pitolisant trial

United States

30 (18 to 65 years old)

Analysis in progress

June 2021 – Oct 2024 11 weeks of follow-up

NCT04886518

Mexiletine (Namuscla)

Mexiletine (Namuscla®) is used to treat myotonia which is characterised by muscle stiffness and difficulty relaxing the muscles. Its use in DM1 is limited as doctors do not have long-term data regarding its safety (particularly with regard to the heart) and efficacy. It is prescribed when myotonia is severe and causes discomfort on a daily basis.

Namuscla® in France

Mexiletine is sold by the pharmaceutical company Lupin under the name Namuscla®. Since June 2021, it has been available in France as part of the "cadre de prescription compassionnelle" [a French compassionate access scheme] for the treatment of myotonia in myotonic dystrophies in adults. Namuscla® is now available from pharmacies with a prescription from a hospital doctor.

▪ Neurologists and cardiologists from specialist centres in France published an article to help cardiologists monitoring DM1 patients decide whether or not to prescribe mexiletine.
Although data from DM1 patients treated with mexiletine published in medical literature is reassuring, its use comes with the need for close cardiac monitoring (cardiac evaluation before starting treatment followed by a yearly checkup).
The onset of any new cardiac symptoms should lead to the benefits of the treatment being reassessed with your cardiologist and neurologist.
Wahbi K et al. Arch Cardiovasc Dis. 2024

▪ The pharmaceutical company Lupin is sponsoring a trial in children and adolescents with myotonic disorders (DM1 and DM2 as well as non-dystrophic myotonias). The trial has two stages. The first stage is currently being conducted in adolescents between the ages of 12 and 17 and will be followed by a second stage (results permitting) in children between the ages of six and 12.

Trial of Namuscla® in myotonic disorders

Phase III
Efficacy

France

12
(6 to 17 years old)

Recruiting

June 2021 – April 2023
56 days of follow-up

2019-003758-97

New treatment avenues

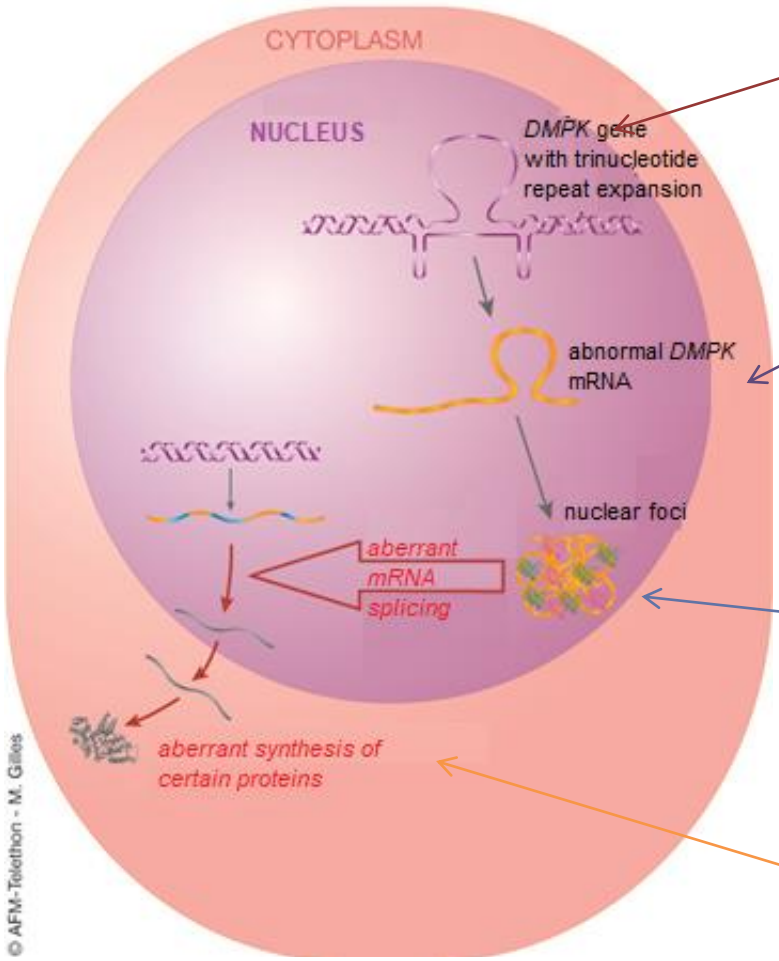
Advances in understanding the mechanisms of DM1 allow different treatment avenues to be explored.

These treatment avenues must first be tested and approved in cell and animal models of the disease before they are allowed to be evaluated in humans in clinical trials.

Treatment avenues currently being studied in myotonic dystrophy type 1 target:

- abnormal *DMPK* gene DNA (and CTG repeats),
- abnormal RNA (and CUG repeats),
- nuclear foci and sequestered proteins,
- the consequences of these abnormalities on cell function.

Prominent treatment avenues in DM1



• Targeting abnormal *DMPK* gene DNA
CRISPR/Cas9, small molecules

• Targeting abnormal *DMPK* RNA
Antisense oligonucleotides (DYNE-101, etc.), siRNAs (del-desiran, etc.), small molecules

• Targeting regulatory protein disruption
Gene therapy (decoy protein, etc.), microRNA (ATX-01, etc.)

• Targeting proteins with impaired synthesis
Verapamil

Targeting the *DMPK* gene

Several approaches looking at how to reduce the abnormally high number of CTG repeats in the *DMPK* gene are currently being studied. They use either the CRISPR/Cas9 system (a new, highly effective tool used to modify targeted genetic information) or small molecules.

▪ A Belgian team evaluated a new method called CRISPR interference with the aim of blocking gene expression and slowing down the synthesis of *DMPK* mRNA from its gene. This approach reduced splicing defects when tested in cells taken from DM1 patients.
Porquet F et al. Mol Ther Nucleic Acids. 2023

▪ Japanese researchers identified a compound called CWG-cPIP which binds to "hairpin" structures that DNA takes on at CTG repeats, preventing them from being copied during *DMPK* mRNA synthesis. This was demonstrated in cells taken from people with DM1 or another trinucleotide repeat disorder called Huntington's disease.
Ikenoshita S et al. J Clin Invest. 2023

Targeting *DMPK* RNA

Five approaches which aim to release proteins that have become trapped in nuclear foci by targeting mutated *DMPK* RNA are already being trialled in humans. Others are still being developed in laboratories.

▪ Results from two approaches that were successfully evaluated in cell models of DM1 were published in the last 12 months.
➔ A gene therapy product consisting of a U7 small nuclear RNA (U7snRNA) containing an antisense oligonucleotide inserted into an AAV8 vector which binds to *DMPK* mRNA at several sites led to a decrease in nuclear foci and splicing abnormalities due to the release of the MBNL1 protein.
CF Almeida et al. Front Cell Dev Biol. 2023

➔ A molecule derived from perimidin-2-amine diazirine binds to and eliminates CUG repeats in *DMPK* RNA which prevents the splicing defects that are characteristic of DM1.
Gibaut QMR et al. ACS Cent Sci. 2023

▪ At the 2023 Annual Meeting of the ASGCT (American Society of Gene and Cell Therapy), Sanofi researchers presented an artificial microRNA inserted into an AAV vector which targets *DMPK* RNA (amiRDMPK). A single injection of this gene therapy product brings about a sustained production of amiRDMPK, meaning that its potential benefits last for a long time.
Intravenous administration of the product in a mouse model of DM1 decreased the amount of *DMPK* RNA in muscle and cardiac cells, reducing damage to these organs, and prolonged the survival of the animals treated.
Tomassy G et al. Abstract 1042 - Annual Meeting of the ASGCT 2023

Adeno-associated viruses *(AAVs) are small DNA viruses that can infect humans. They are used in genetic engineering as vectors for gene therapy.*

Targeting disrupted regulatory proteins

In DM1, abnormal nuclear foci sequester MBNL regulatory proteins, making them less available which in turn causes numerous disturbances in muscle cells. MBNL proteins regulate the splicing of various different RNA molecules and therefore influence the activity of several other cell proteins.

▪ A Spanish team (which is already involved in the development of ATX-01 through a collaboration with ARTHEx Biotech) developed synthetic microRNAs which inhibit two natural microRNAs that regulate MBNL1 protein synthesis: miR-23b (the target of ATX-01) and miR-218. Their chemical composition has been optimised to make them more efficient and less toxic (phosphorodiamidate morpholino oligomer or "PMO").
When administered intravenously to mice with DM1, they increased MBNL1 synthesis at relatively low doses and reduced myotonia.
González-Martínez I et al. Mol Ther Nucleic Acids. 2023

Repurposed drugs

▪ A team from Quebec showed that senescent cells produce and disseminate potentially harmful molecules in muscle.

Targeting stem cells to repair muscles?
By dividing, stem cells enable new cells to be created which are able to regenerate damaged organs. In DM1, certain stem cells in muscles stop dividing prematurely and slowly degrade. This is referred to as senescence, a process that plays a role in aging.

Administering senolytics (which specifically destroy senescent cells) to muscle cells enables functional stem cells to repair muscle.
Conte TC et al. Nat Commun. 2023

▪ JUV-161 is a drug candidate developed by Juvena Therapeutics which has been granted orphan drug designation in the United States. It targets signalling pathways involved in the survival and regeneration of muscle cells (MAPK/ERK and PI3K/AKT).
JUV-161 improved muscle strength and mass in mice with DM1.
Kim HJ et al. - MDA Clinical & Scientific Conference 2024

*Cell **signalling pathways** enable messages to be sent to cells to modulate their activity (growth, division, differentiation, death, etc.). A message can come from other cells in the body or from the external environment. Its arrival at a cell receptor triggers a cascade of reactions that change the cell's behaviour.*

▪ Intramuscular administration of boldine (a molecule used to aid digestion) reduced myotonia in mice with DM1, confirming interesting results obtained from fly models of DM1 and cells taken from DM1 patients.
Álvarez-Abril MC et al. Int. J. Mol. Sci. 2023

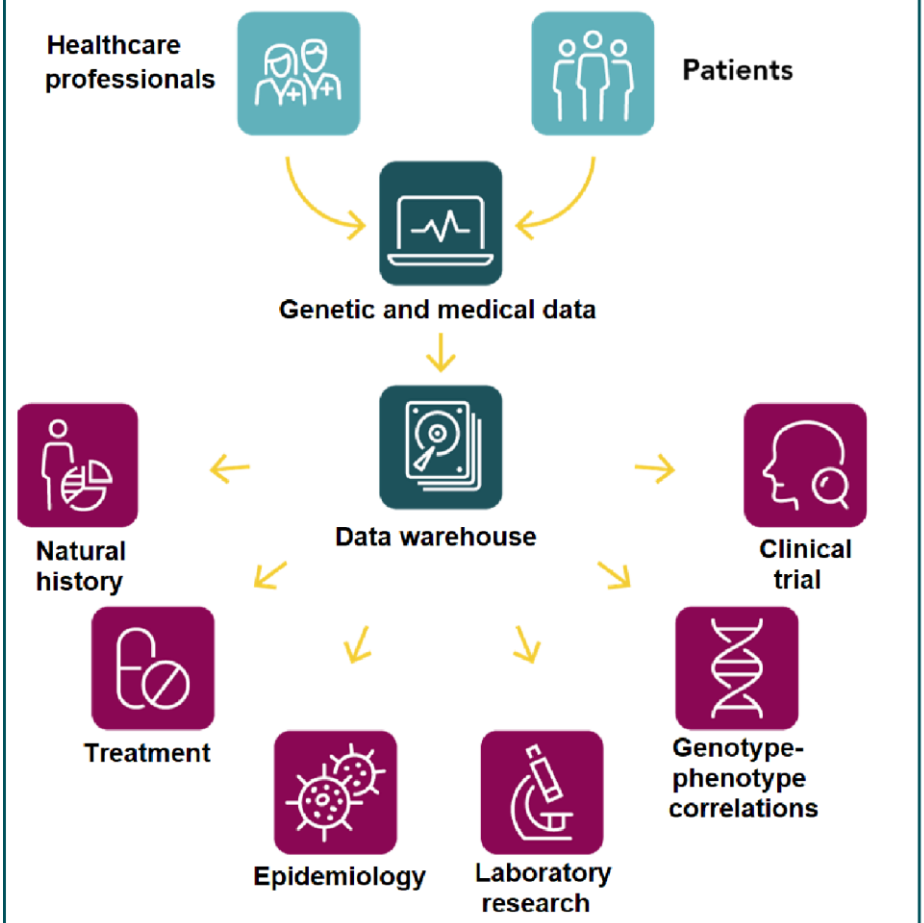
▪ Having shown that simultaneous poor calcium and chloride channel function contributes significantly to skeletal muscle damage in DM1, researchers have suggested looking into specific calcium channel blockers such as verapamil to alleviate DM1 symptoms.
Cisco LA et al. J Clin Invest. 2024 Jan

Tools for future trials

Data warehouses

Developing patient databases makes it possible to carry out censuses (which are exhaustive when conducted in registries) of people with the same disease, determine the natural history of the disease, establish genotype-phenotype correlations and recruit participants to clinical trials.

Registries and databases
A patient registry or database is a collection of genetic and medical data from people with the same disease (with their consent).



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, etc.).*
They help to identify whether a relationship exists between the presence of a genetic mutation and the manifestations of a genetic disease.

The DM-Scope registry

The DM-Scope registry, supported by AFM-Téléthon, was set up in France in 2008 to collect data from people with myotonic dystrophies and facilitate clinical research in these diseases. It has since become the world's largest myotonic dystrophy database.

- DM-Scope currently collects demographic, clinical and laboratory test data from 3,828 people with myotonic dystrophies (3,551 DM1 patients and 263 DM2 patients).

In collaboration with 55 specialist neuromuscular disease centres, it has been the foundation for 12 clinical trials (observational studies, basic research, etc.).

www.dmscope.fr/french-registry-of-myotonic-dystrophies/

DM-Scope registry

France | 3,828 patients | Recruiting | Created in January 2008

The iDM-Scope project

A French-Québécois consortium called iDM-Scope created an international platform for myotonic dystrophies in order to facilitate the implementation of multisite trials, conduct natural history studies, identify biomarkers and develop potential treatments.
Set up in July 2016, it brings together the DM-Scope registry and a Québécois database that covers the Québec City and Saguenay region.

*A **biological marker** (or **biomarker** for short) is a measurable characteristic that indicates a normal or pathological biological process. 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, etc.) or molecular (change in the expression of a protein, etc.).*

iDM-Scope registry

Canada | 1,410 patients | Recruiting | Created in 2002

Identifying the best endpoints

It is important to have easy-to-use tools that help to identify the beneficial effects of a drug candidate on a restricted number of patients (since DM1 is a rare disease) over a limited period of time (the disease progresses slowly) - usually around one year.

▪ **Titin** is an abundant protein in muscle. Its levels in urine are being studied as a potential biomarker in several neuromuscular diseases, especially since the test involved is easy to carry out. Its levels are higher in DM1 patients and, according to an analysis of urine samples from 29 DM1 patients, may correlate with the severity of muscle damage.
Before this potential biomarker can be used in clinical trials, it is essential to know how titin levels vary over time and as the disease progresses, and to reproduce these results in a larger number of patients.
Varga D et al. Muscle Nerve. 2023

▪ Analyses of muscle biopsies from 11 DM1 patients led to six new proteins being proposed as potential biomarkers of muscle damage in DM1.
Aoussim A et al. J Neuromuscul Dis. 2023

▪ An international study is currently underway to identify the best biomarkers by monitoring 700 DM1 patients for two years. Fifteen investigator sites are participating in this study, including the Institut de Myologie (Paris).

END-DM1 trial

France and abroad | 700 (18 to 70 years old) | Enrolling by invitation | Jan 2019 – Feb 2025 2 years of follow-up

NCT03981575

▪ Another study is currently taking place to find and monitor microRNA biomarkers for four years.

RNA biomarkers in blood and urine

United States	215 (over 5 years old)	Recruiting	Dec 2020 – Dec 2025 4 years of follow-up

NCT05020002

MicroRNAs (miRNAs)
MicroRNAs are present in blood and urine and can be easily detected.

Better management of the disease

Multidisciplinary care

__Smooth muscle__ is found in the walls of blood vessels, the digestive tract, the urinary tract and some organs. This type of muscle contracts involuntarily. Its organisation is different to that of skeletal muscle (which is under voluntary control).

DM1 can affect other parts of the body (the heart, respiratory system, central nervous system, etc.) as well as the muscles. Non-muscular symptoms (such as bowel problems) can have a significant impact on quality of life.
They can occur at a certain point during the course of the disease in one patient and appear later, earlier or even not at all in another patient.

▪ A study showed that the majority of 58 children with DM1 felt that gastrointestinal and urinary problems impacted their daily lives: abdominal pain (52%), swallowing problems (42%), diarrhoea (36%), constipation (33%), urinary incontinence (22%), potty training problems (60%), etc. In 22% of cases, their parents classified the impact of these issues as severe, sometimes resulting in feelings of shame, absences from school and limiting family activities.
Maagdenberg SJM et al. Neuromuscul Disord. 2023

Don't be afraid to share
During your follow-up appointments, it is important to mention any problems or discomforts you may be experiencing, even if they don't seem to be related to your disease. This will enable your doctors to provide you with the best care.

The __thyroid__ regulates several functions in the body by influencing the metabolism. For example, it is involved in regulating body temperature, heart rate, digestion, mood, etc.

▪ A retrospective study of 3,842 DM1 patients showed that they had an increased risk of **endocrine** (hormonal) **disorders**: diabetes (in 15% of patients) or thyroid dysfunction (18%).
These disorders, which are already known to be present in DM1, generally progress independently of the muscle impairment caused by this disease and benefit from being treated by an endocrinologist.
The study also showed that **cataracts** occurs earlier in DM1, as demonstrated by the fact that surgery was required around the age of 55 on average compared to 69 in the general population.
Finally, the study showed that the **risk of cancer** was nearly two times higher than in the general population. Over the course of six years, 12% of the patients were diagnosed with cancer.
Other studies have already reported that DM1 patients have a higher risk of developing cancerous or benign tumours. That said, it is difficult to know whether there was influence from other risk factors (smoking, overexposure to the sun, etc.) in these studies.
Seo I et al. Neurol Sci. 2024

Essential screening
Cancer screening guidelines in DM1 are the same as for the general population. Regular checkups and screening tests specific to certain cancers (mammogram, faecal immunochemical test, etc.) enable the most common types to be diagnosed early.
Make sure you report any worrying signs to your doctor (presence of blood in your stool, unexplained weight loss, a new mass/lump in your breast, persistent cough, change in the appearance of a mole, etc.). When cancer is detected early, it can be treated more effectively and with less harsh treatments.

▪ In France, a retrospective study (COSMOS-France) is planning to study the presence of disorders associated with DM1 by combining data from the DM-Scope registry and the Système National des Données de Santé [French National Healthcare Data System].
Vertex patient information leaflet - COSMOS France project [page in French]

Cardiac care - a lifelong necessity

Heart complications contribute to the severity of DM1. They generally consist of cardiac conduction disorders or arrhythmias with a significant risk of sudden death if they are not treated (with a pacemaker or implantable cardioverter defibrillator, for example).

▪ A natural history study of cardiac involvement in nearly 200 adolescents and adults with DM1 showed how important long-term cardiac monitoring is. In 10 years, the percentage of patients with cardiac involvement gradually increased from 42% to 66%. This cardiac involvement can even go unnoticed (only 17% of the patients reported cardiac symptoms).
Helle Petri H et al. Int J Cardiol. 2024

*An **arrhythmia** is an abnormality in the heart's rhythm, which may beat too fast (tachycardia), too slowly (bradycardia) or irregularly. Symptoms include feeling faint, palpitations, etc.*

*A **cardiac conduction disorder** is a problem with the electrical system in the heart. They can cause the heart rate to speed up (tachycardia) or slow down (bradycardia), or even brief pauses where the heart stops beating for a few moments, resulting in dizziness, momentary fatigue, or temporary loss of consciousness.*

Electrocardiograms (ECGs) are used to help diagnose these conditions. Some are harmless and do not need to be treated while others require medication to be taken or a pacemaker/ICD to be fitted.

Regular cardiology checkups are essential
It can be difficult to get DM1 patients to see a cardiologist and have an ECG every year when they usually have almost no symptoms. However, the potential seriousness of cardiac involvement in DM1 is not proportional to the severity of limb muscle impairment. Regular checkups enable suitable treatment to be started as soon as any cardiac abnormalities are detected.

▪ A Japanese study identified several genetic factors (other than those associated with the *DMPK* gene) which may be linked to the risk of sudden death. These findings, obtained from three people with DM1 who suffered sudden death, need to be confirmed in a larger number of subjects.
Hata Y et al. J Neurol. 2023

A risk of circulatory conditions

French doctors have reported that DM1 increases the risk of deep vein thrombosis (when a blood clot forms in a vein in the leg) and pulmonary embolism (when a blood clot travels to and blocks an artery in the lungs). These conditions are referred to as "venous thromboembolisms".
A clinical trial supported by AFM-Téléthon is currently underway to better understand the mechanisms involved and improve prevention of these conditions.

Venous thromboembolism in DM1

France

130 (over 18 years old)

Recruiting

June 2018 – Dec 2024
2 years of follow-up

NCT03424460

Non-invasive ventilation

Respiratory insufficiency *is a condition in which the lungs are unable to supply oxygen and/or remove carbon dioxide from the blood. Depending on how severe it is, it may cause no symptoms at all or manifest as excessive shortness of breath on exertion, repeated bouts of bronchitis or waking up with headaches. Respiratory insufficiency can be detected using tests such as arterial blood gas analysis or lung function tests, the results of which help determine how it should be treated (respiratory physiotherapy, medication, ventilation, etc.).*

Respiratory problems can develop gradually in DM1 without the patient realising (temporary breathing difficulties, ineffective cough, recurrent chest infections, headaches or sweating (especially when waking up), difficulty gaining or losing weight, fatigue, etc.).
Regular checkups are able to detect these problems so that non-invasive ventilation (NIV) can be administered. There is currently no consensus on when to start NIV.

▪ German researchers developed a method to make it easier to detect breathing problems in DM1 patients. It involved completing a 27-item checklist (the "Respicheck") together with clinical assessments and lung function tests. A validation study conducted in 172 people (including 74 with DM1) demonstrated that this method was able to identify patients who required ventilation.
Gutschmidt K et al. Neuromuscul Disord. 2023

▪ NIV can be inconvenient and difficult to live with. Many patients do not use it enough. Out of 101 Dutch patients monitored for a year who had been prescribed NIV, 58 had low treatment adherence. These results are consistent with those from other similar studies. An analysis of the possible causes of this low treatment adherence did not reveal any specific determining factors, and there were no differences between patients (with low or high treatment adherence) in terms of respiratory function. It is therefore very difficult to identify people at risk of non-adherence to NIV in advance.
Vosse BAH et al. Neuromuscul Disord. 2023

Ventilation *consists of helping or replacing the function of the lungs in a patient whose breathing is failing using a machine called a ventilator.*

Starting ventilation treatment

Ask your doctor to explain the advantages and disadvantages of ventilation treatment in everyday life and make sure that you ask questions and voice your concerns. Preparing for the upcoming changes in your everyday life will help this treatment be implemented more smoothly.
If you experience any problems, report them straight away. There are always ways in which the comfort and efficacy of ventilation treatment can be improved.

▪ A study is currently taking place in France (Lille) to better characterise respiratory impairment in DM1. It is researching factors associated with alveolar hypoventilation (a decrease in the volume of air circulating in the alveoli in the lungs) such as respiratory function, cognitive impairment, daytime sleepiness, etc.

Factors associated with hypoventilation in DM1

France	160 (over 18 years old)	Recruiting	June 2010 – Sept 2023 5 years of follow-up

NCT03764150

Cognitive impairment - from assessment to management and treatment

The central nervous system

Several different types of exams, first and foremost magnetic resonance imaging (MRI), can detect central nervous system abnormalities but are not able to precisely identify their effects.
Although the mechanisms are poorly understood, we do know that central nervous system abnormalities in DM1 contribute to cognitive impairment, sleep disorders and motor impairment (walking and balance problems).

*The **central nervous system** is made up of the brain (the cerebrum, cerebellum and brain stem) and the spinal cord. It is protected by the skeleton (the skull for the brain and the spine for the spinal cord). It controls cognitive functions (thoughts, speech, memory, etc.), analyses sensory information, coordinates movement and orders muscles to contract.*

A document written by healthcare professionals and the AFM-Téléthon Groupe d'Intérêt Steinert (DM1 & DM2) was published in May 2024.
Cognitive impairment and mood disorders in DM1 - better understanding for a better response [document in French]

In adults

- A French study conducted in 124 adults between the ages of 19 and 73 revealed three types of cognitive profile:
  - 68% (mainly the younger patients) showed no signs of cognitive impairment,
  - 23% had cognitive impairment which was mainly affected their executive functions (a set of skills that help an individual plan and organise, multitask and execute their goals),
  - 9% had more pronounced and diffuse cognitive impairment.

These observations suggest that there may be cognitive decline and a neurodegenerative process that progresses with age and are consistent with the results of a Japanese study conducted in 67 adults with DM1.
Davion JB et al. J Neurol. 2024 *Fujino H et al. J Neuromuscul Dis. 2023*

- A study is currently taking place in France (Lille) to evaluate the link between white matter abnormalities visible on MRI and cognitive impairment, and to look for possible causes of this cognitive impairment (diabetes, accumulation of tau protein which is known to be toxic in other neurological diseases).

MD-VASCOG trial

France	150 (18 to 75 years old)	Recruiting	Oct 2021 - Jan 2029 4 years of follow-up

NCT04656210

A move towards new tests?

Several different tests are used to characterise cognitive function which have been somewhat adapted to DM1 patients who get tired easily. Online tests are currently being looked at to replace some pen and paper tests used in DM1.
Fortin J et al. Neuromuscul Disord. 2023

In children

Three studies (conducted in 55, 45 and 27 children respectively, most of whom had the congenital-onset form of DM1) have helped to better characterise cognitive impairment in children.

▪ Cognitive impairment can manifest as intellectual disability as well as impaired attention, working memory (ability to retain and use information in the time necessary to carry out a task), executive functions (determining what needs to be done to achieve a goal, changing tactics, going from one task to another, etc.), spatial reasoning (ability to orient yourself in space, determine the distance between two objects, etc.) or ability to recognise and understand emotions.

A cognitive assessment performed by a neuropsychologist is essential for identifying a child's strengths and weaknesses so that the best strategies can be chosen to help compensate for their difficulties and tailor their schooling.

Patel N et al. Neurology. 2024
Sweere DJJ et al. Muscle Nerve. 2023
Aden P et al. Eur J Paediatr Neurol. 2023

***Cognitive remediation** is a type of individual or group therapy that involves learning how to manage the impact of cognitive impairment in everyday life. It can be undertaken at any age and involves various different types of healthcare professionals (psychologists, neuropsychologists, speech and language therapists, occupational therapists).*

***Cognitive behavioural therapy (CBT)** is a type of therapy which helps resolve everyday problems by addressing behaviours or fears, even phobias, which make these problems worse. This approach can be personalised and adapted to each individual's goals.*

Possible treatments

Cognitive remediation therapy (CRT) helps patients improve their cognitive abilities and translate the skills they learn into their daily lives. Cognitive behavioural therapy (CBT) helps patients find solutions to problems that they may encounter in their everyday lives.

A study of social and emotional remediation using virtual reality is currently taking place in the Île-de-France region of France in children and adolescents with congenital-onset DM1.

Impact on social life

Some DM1 patients can experience impairments in their social cognition (a set of cognitive processes that enable us to have social interactions) which can lead to difficulties in interpersonal relationships and be the source of severe social isolation. They can also be the source of embarrassment and misunderstandings at work and in their daily lives (failing to understand a harmless joke or misunderstanding).

Theory of mind is a well-studied field of social cognition. It is the capacity that allows us to ascribe mental states to others and to ourselves (for example, understanding when someone is sad).

According to a French study conducted in 50 DM1 patients, the impairments in social cognition found in DM1 are usually the result of impairments in affective theory of mind (expressing feelings and recognising the emotions and desires of another person) rather than cognitive theory of mind (understanding that others have different thoughts and ideas, understanding the logic of another person).

They also correlate with brain abnormalities seen on MRI scans performed on DM1 patients.

Davion JB et al. Cortex. 2023

▪ A Dutch study evaluated five diseases (including facioscapulohumeral muscular dystrophy and DM1) and found that the lack of facial expression seen in these conditions often had a negative impact on social interactions. Several strategies were reported that helped patients compensate for this, including exaggerating facial muscle movements in order to display an emotion more clearly and teaching their family and friends about their disease and its symptoms.

Rasing NB et al. Disabil Rehabil. 2023

Exercise

Several studies have demonstrated the validity and effectiveness of exercise training programmes on combating deconditioning and the fatigue it causes.

- Two studies conducted in around 10 patients showed that a 12-week gentle strength-training programme also produced visible results at a cellular level. It seemed to improve mitochondrial function and may even reduce DM1-associated splicing events.
Davey EE et al. JCI Insight. 2023
Valeria Di Leo V et al. J Neuromuscul Dis. 2023

- A trial that involves completing a four-month at-home exercise training programme with or without taking a dietary supplement is due to take place in Canada and will include 40 DM1 patients and 20 healthy subjects.

***Deconditioning syndrome** is defined as a decline in physical function (heart, lungs, muscles) that occurs following prolonged inactivity. It manifests as fatigue and fatigability which leads to further inactivity and in turn makes the syndrome worse.*

Home-based training and supplementation

Canada

60
(19 to 65 years old)

Not yet recruiting

May 2023 – Jan 2025
4 months of follow-up

NCT05848830

Adapting pain management

Seventeen out of 20 DM1 patients included in a recent Norwegian study reported chronic pain (lasting for more than three months). Six of these patients reported neuropathic pain, a type of pain which is very rarely described in DM1 that causes burning sensations or sharp pains in the feet and requires specific treatment. Fourteen patients reported muscle pain and three reported both muscle and neuropathic pain.
Gro Solbakken G et al. Front Neurol. 2024

Pain and neuromuscular diseases, AFM-Téléthon 2024 reference document
[document in French]

Advances in genetics

The genetic mutation that causes DM1 is the abnormally high number of CTG repeats in the *DMPK* gene. This number is over 50. Generally, the higher the number of CTG repeats (there can be up to 4,000), the greater the number of, the more severe and earlier the onset of the disease's manifestations, although this correlation is not absolute.

The future of genetic diagnosis

Repeat expansions are particularly difficult to sequence. New long-read sequencing techniques which have been in development for a few years are able to sequence challenging regions such as the abnormally high number of CTG repeats in the *DMPK* gene. Although they are used in research, they still have not been approved to be used as a diagnostic tool in DM1.

Owusu R et al. Acta Myol. 2023

DMPK methylation

DNA methylation is an epigenetic modification. It refers to the addition of a methyl (CH3) group to the nucleotide base cytosine and influences gene expression.

It can moderate the effects of the high number of CTG repeats in DM1. According to research, high levels of methylation in the *DMPK* gene seem to be involved in the congenital-onset and adult-onset forms of DM1, while the degree of methylation in the *DMPK* gene seems to be linked to muscle strength.

- Sometimes, the CTG repeats are interrupted by other trinucleotide repeats (CCG or CGG for example). Patients with these variations develop milder symptoms (age of onset, cardiac and respiratory involvement, lack of mobility).

A comparison of 20 patients with these variations and 20 without them showed that there were different methylation profiles in the patients with the variations which may contribute to the variability of symptoms in this disease.

Visconti VV et al. Int J Mol Sci. 2023

- Research carried out on various cell models of DM1 indicates that the excision of CTG repeats in "immature" stem cells also corrects methylation levels. However, methylation levels stayed the same in "mature" differentiated stem cells.

This may mean that approaches targeting this genetic mutation in DNA would not be able to restore the degree of methylation which would limit their effectiveness as they are applied to differentiated cells.

Handal T et al. Nat Commun. 2024

*
* *

Keep up to date with myotonic dystrophy type 1 research news throughout the year on the AFM-Téléthon website:

www.afm-telethon.fr/en

And via the AFM-Téléthon Groupe d'Intérêt Steinert (DM1 & DM2) blog:

steinert.afm-telethon.fr/ [website in French]