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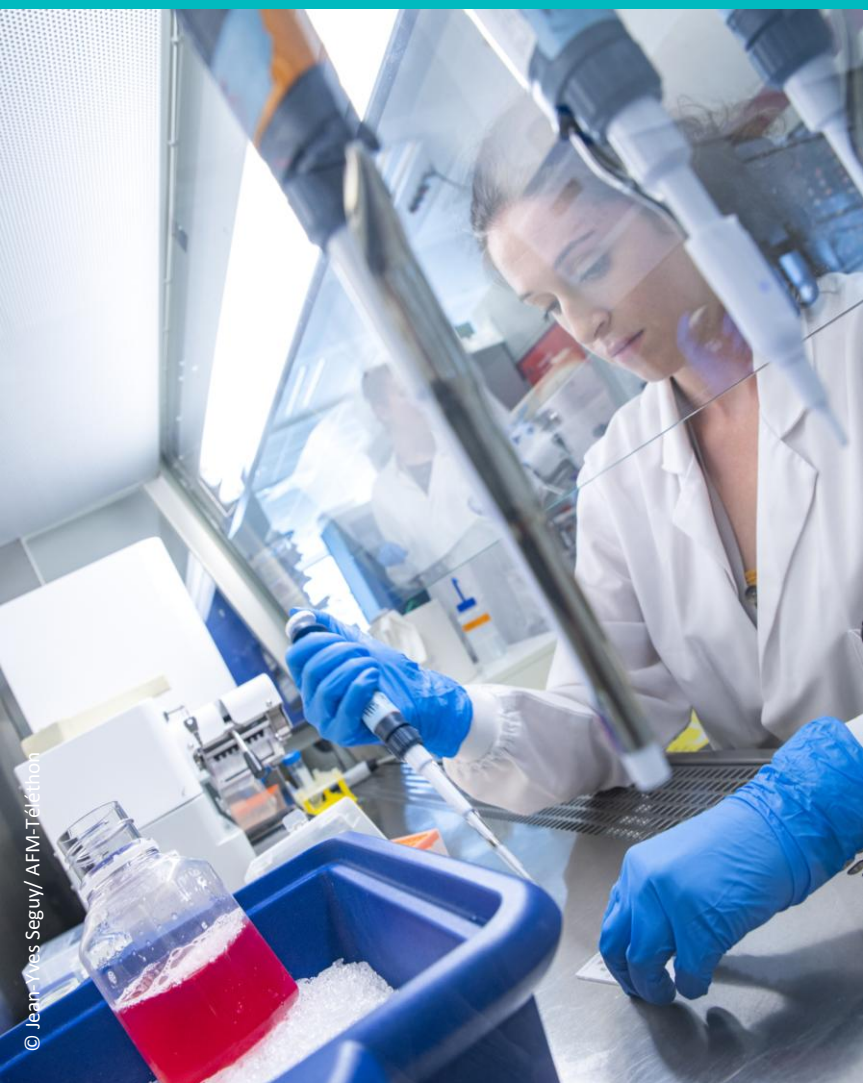
SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2025 in Duchenne muscular dystrophy and Becker muscular dystrophy



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

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

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Every clinical trial described in this document is accompanied by its "NCT" number (written as "NCT0XXXXXXX") - an identification number assigned to each clinical trial on ClinicalTrials.gov, the most comprehensive clinical trials database in the world.

Clicking on these numbers in the document will open the corresponding trial's description page on the ClinicalTrials.gov

Duchenne muscular dystrophy and Becker muscular dystrophy

DMD & BMD

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are two muscle diseases (myopathies) caused by genetic mutations in the gene that codes for **dystrophin**, a protein that stabilises muscle cells. They are also known as "dystrophinopathies". They primarily affect males, but females can also be affected in rare cases.

Common symptoms

- **Progressive striated skeletal** (limbs, torso, respiratory muscles), **cardiac** and smooth **muscle weakness**. This gradually restricts walking ability, and later other movements. The heart and breathing also become less efficient.
- **Cognitive difficulties are common and variable** in both DMD and BMD.
- **A later onset in** BMD (adolescent) than in DMD (around three to four years old), and milder symptoms.

Management and treatment

Corticosteroids (prednisone, deflazacort) delay loss of ambulation and maintain respiratory function (from the age of four to five years old).

Angiotensin-converting-enzyme (ACE) inhibitors limit how hard the heart has to work (from the age of eight to 10 years old in DMD and as early as possible in BMD).

New treatments in fields such as gene therapy (micro-dystrophin), exon skipping, genome editing and cell therapy are currently being developed, some of which have already been authorised (Elevidys®).

But also...
Orthopaedic physiotherapy, respiratory physiotherapy, breathing support, psychological management and nutritional management.

Diagnosis

Clinical diagnosis

Clinical examination by a doctor to look for muscle weakness (legs, arms, torso). Sometimes the presence of cognitive impairment informs the diagnosis.

Genetic and laboratory diagnosis

Creatine kinase (a muscle enzyme) blood test.
Muscle biopsy to determine the type of muscular dystrophy and to look for the absence (DMD) or abnormal quantity/quality of dystrophin (BMD).
Genetic testing to look for *DMD* gene mutations.

In numbers

DMD: 1 in 5,000 male births **BMD: 1 in 18,000 to 31,000** male births (*orpha.net*)

792 scientific articles published between June 2024 and June 2025 *(PubMed)*

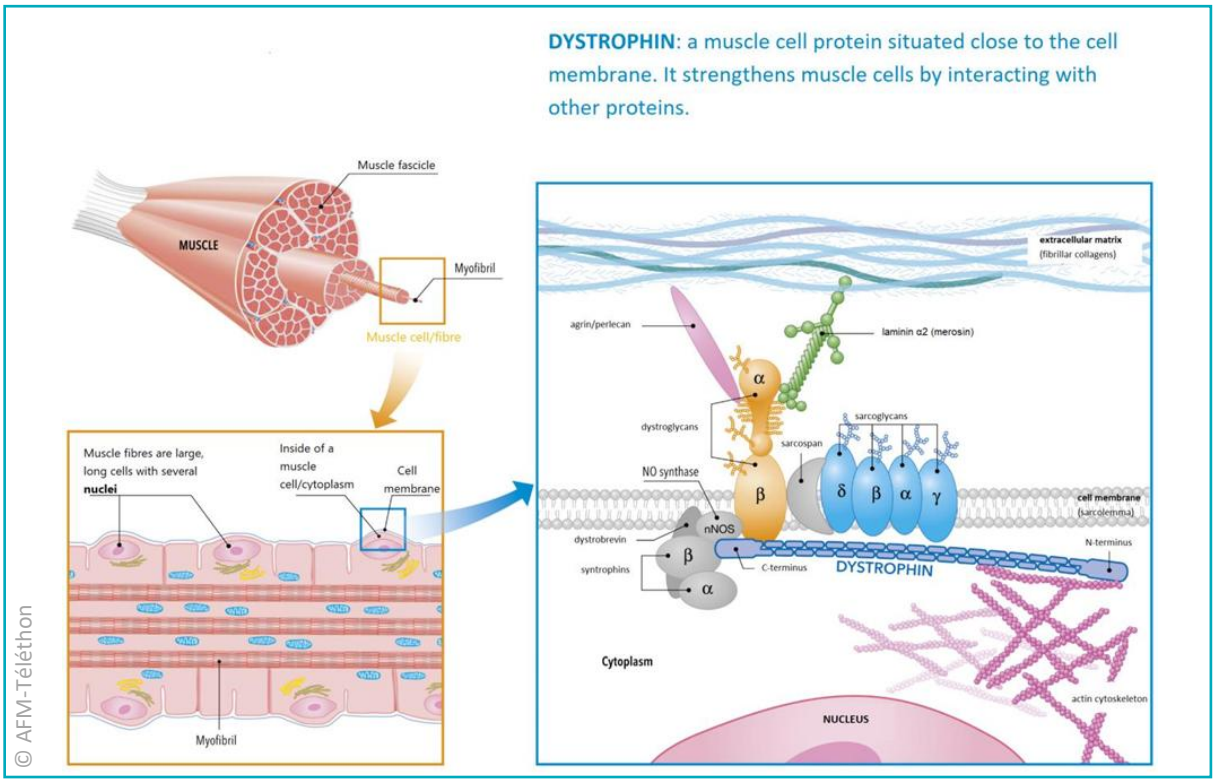
122 clinical trials and observational studies currently underway, including **13** in France *(ClinicalTrials.gov 23/06/2025)*

What causes DMD and BMD?

☑ Mutations in the dystrophin-coding *DMD* gene, which is located on the X chromosome.

Duchenne muscular dystrophy
No dystrophin is produced

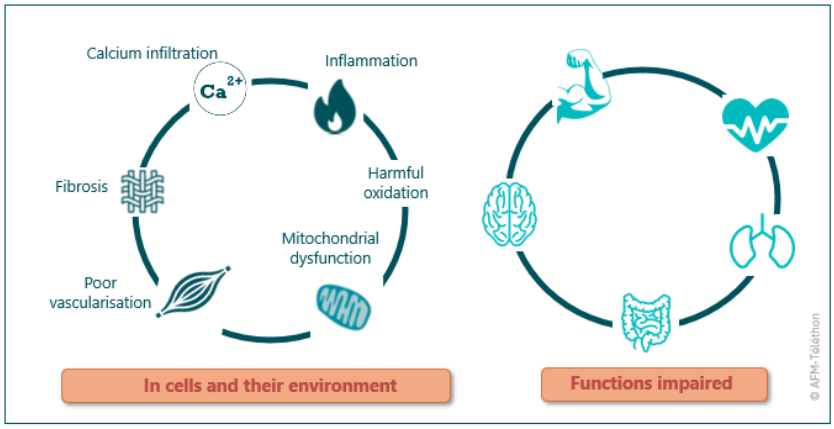
Becker muscular dystrophy
Little dystrophin is produced or dystrophin is smaller and only partially functional



Effects on cells and functions

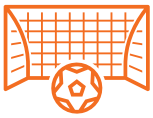
☑ The absence (DMD), partial deficiency and reduced size (BMD) of **dystrophin** all weaken the membrane of muscle cells.

☑ **Disturbances** such as calcium overload, oxidative stress, mitochondrial dysfunction, chronic inflammation, less efficient muscle regeneration and fibrosis follow, causing a progressive loss of muscles and their mechanical function. Other types of tissue (other than muscle) are also affected.



For more information on DMD and BMD, please visit:
www.afm-telethon.fr/fr/fiches-maladies/dystrophie-musculaire-de-duchenne [page in French]
www.afm-telethon.fr/fr/fiches-maladies/dystrophie-musculaire-de-becker [page in French]
www.afm-telethon.fr/fr/fiches-maladies/dystrophinopathies-chez-les-femmes [page in French]

4 highlights from the past 12 months



Nearly there for micro-dystrophin gene therapy in France

GNT0004, an AAV micro-dystrophin gene therapy product developed by Généthon, was evaluated in the first part of a phase I/II/III clinical trial. The product was well tolerated and produced positive results in terms of motor function one year and two years post-treatment in the children who received the second dose (3 x 10^{13} vg/kg) during part 1 of the trial. These results have enabled the trial to move into its pivotal phase (confirming the product's efficacy in a larger number of patients and comparing it to a placebo), the start of which is imminent (sites in France). Learn more.

New drugs that protect muscle

- Givinostat, a new drug that aims to reduce fibrosis and inflammation in DMD, is now available in France for ambulatory boys over the age of six via compassionate access. It has been granted conditional marketing authorisation in Europe. Learn more.
- Vamorolone is an anti-inflammatory drug that has been authorised in Europe but is not available in France. Learn more.

A better understanding of cognitive impairment

More and more data obtained through new studies and collaborative projects concerns cognitive impairment in DMD and BMD, recognised as being associated with these diseases. This impairment and its links to the absence of certain forms of dystrophin in the brain are now better characterised. This work and knowledge should help improve screening for cognitive impairment using approved tools, and promote the wider use of drugs available to treat it. New gene therapies could make it possible to treat both the muscles and the brain. Learn more.

Initial preclinical results for innovative tools

- Researchers have shown than producing nearly full-length dystrophin in muscle from several gene fragments, transported by adeno-associated viral (AAV) vectors, is possible with the help of inteins, and that it is effective in mice. Learn more.
- Applied to the dystrophin gene, genome editing involves directly modifying a *DMD* gene mutation in order to produce dystrophin. It is starting to produce positive results in animal models and preclinical studies, particularly for exon skipping. Learn more.

Therapeutic approaches in DMD and BMD

Addressing the absence of dystrophin and limiting its consequences

- **Producing dystrophin in muscle**

Gene therapy, exon skipping, genome editing and stop codon readthrough are techniques that aim to provide muscle cells with the genetic tools for making dystrophin or a version close to it.

- **Promoting muscle regeneration**

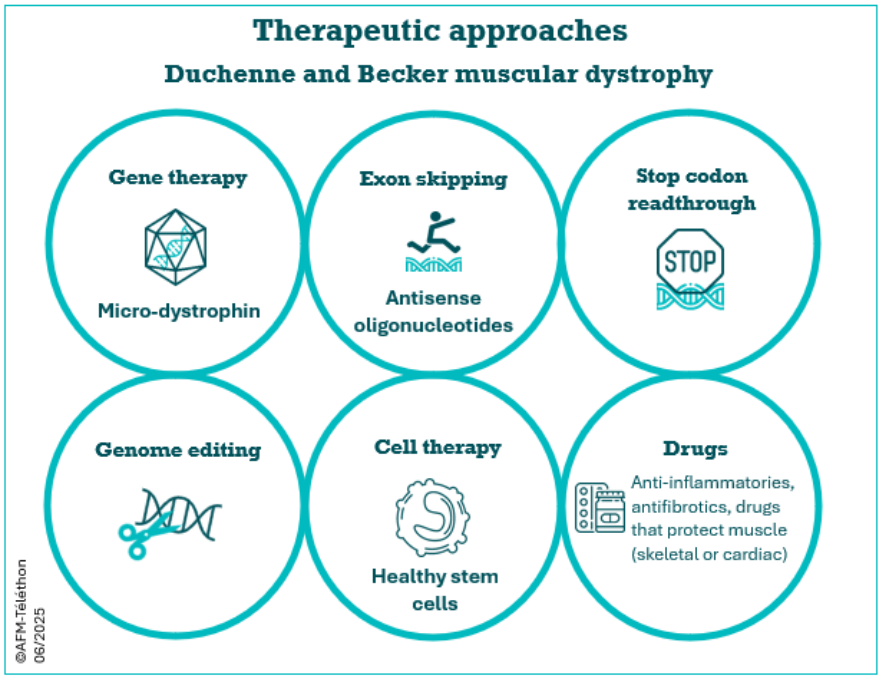
Cell therapy techniques are designed to provide patients with healthy stem cells that rebuild target tissues such as muscle.

- **Responding to the consequences of the absence of dystrophin**

More traditional drugs target inflammation, fibrosis and the muscle fibres themselves in order to protect the integrity of the muscles and prevent them from deteriorating.

Gene therapy *refers to any technique that introduces genetic material into the body in the form of DNA or RNA (therapeutic genes, antisense oligonucleotides, etc.) for therapeutic purposes.*

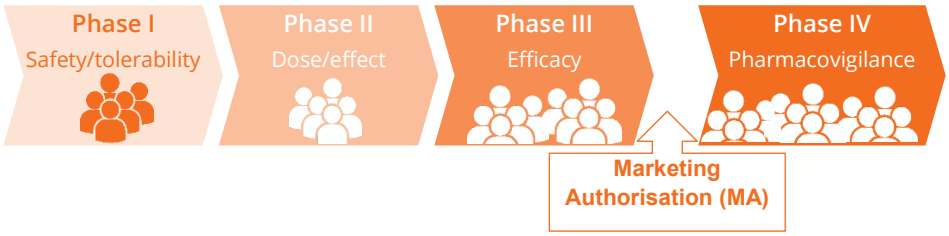
Cell therapy *uses living cells. This approach consists of taking cells either from the patient to be treated or a donor, purifying them, modifying them if necessary and then multiplying them. These cells are then put back into the patient to replace deficient or missing cells.*



Clinical trials - an essential step

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. If the evaluation is positive, the pharmaceutical company can apply to regulatory authorities such as the European Medicines Agency (EMA) for marketing authorisation (MA). 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 side effects that may occur.

"Real-life" *observational studies are conducted without altering the patients' treatment. They make it possible for data to be collected on the course of the disease and for it to be monitored in "real life" using different sources such as connected objects, patient questionnaires, medical records and reimbursements for care.*



Inclusion criteria in clinical trials - how do they work?

Unique to every clinical trial to help ensure their quality

▪ Inclusion criteria define the population of patients who can participate in a given trial. They are strict in order to ensure that homogeneous groups of patients are formed. Reducing the gaps between the clinical profiles of individuals provides the best chance of being able to observe a so-called "significant" (statistically) therapeutic effect of the product and makes it possible to limit background noise linked to other factors such as the individual course of the disease.

And in DMD and BMD?

The inclusion criteria in DMD and BMD trials typically include genetic mutation, age, sex, and indicators of motor function (ambulatory or non-ambulatory, six-minute walk test, NSAA scores, PUL scores, etc.) and physiological function (lung function, cardiac health, etc.). If you or your child would like to participate in a trial, these criteria will be evaluated at the investigator site where the trial is taking place using a series of assessments in order to determine whether participation in the trial is possible.

The North Star Ambulatory Assessment (NSAA) *scale measures a patient's ability to perform various tasks (walking, running, jumping, climbing stairs, getting up from the floor, etc.). This scale provides a fairly accurate interpretation of the experiences of patients in daily life.*

Can a patient still be included in a trial even if they don't meet all the criteria?

Unfortunately not. For example, a protocol designed for ambulatory boys with DMD aged six to 10 years old cannot include five-year-old boys, non-ambulatory boys, or symptomatic girls. It is not the doctor at the investigator site who decides, but the criteria of the trial which must be met.

However, trials are only one step in the development of a drug. If the results of a clinical trial are positive for a product in a certain indication (disease, age, situation), this paves the way for other clinical trials, or even access to the drug for a larger population via an early access programme such as the one that exists in France.

Les essais cliniques en pratique [Clinical trials explained]

Several challenges to overcome

During a webinar organised by the AFM-Téléthon Groupe d'Intérêt Duchenne-Becker, Serge Braun, former scientific director of AFM-Téléthon, was encouraging about the latest therapeutic advances in DMD, while detailing the challenges in treating this rare and complex disease, particularly through gene therapy approaches which are long and costly. In particular, he highlighted:

▪ the fact that muscles (the first part of the body to be affected by the disease) represent 40% of the body's weight which must be reached and treated;

▪ the need to also treat other affected organs (heart, smooth muscle, central nervous system) and to find suitable vectors in order to be able to do so;

▪ the challenge of the very large size of the *DMD* gene which requires finding molecular tricks to deliver it;

▪ the severe inflammatory component of the disease which requires the management of the possible side effects of innovative treatments;

▪ the limited regeneration and fibrosis requiring early treatment before there is too much damage;

▪ the slow progression of the disease which complicates the observation of the effects of a drug over a short period of time (often restricted in clinical trials), while positive effects could be revealed over a longer period.

Webinar "Une heure avec [An hour with]" S. Braun, Groupe d'Intérêt Duchenne-Becker, AFM-Téléthon, 22 May 2025

A quick look - trials, studies and registries

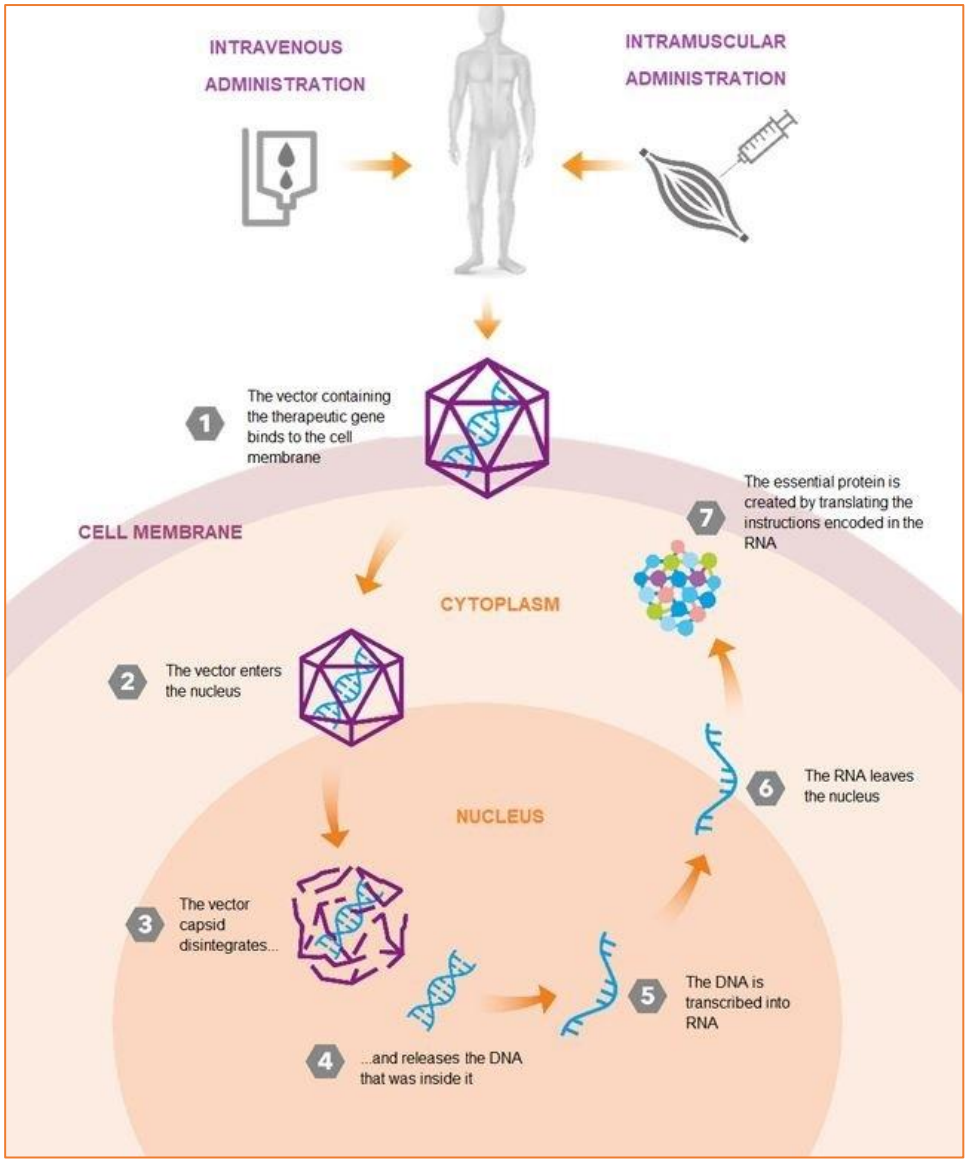
Clicking on the underlined links takes you to the product page in the document.

APPROACH	DRUG CANDIDATE	TRIALS	LOCATION
Restoring dystrophin expression			
Micro-dystrophin gene therapy	• GNT0004 (Généthon) • SRP-9001 (Sarepta) • SGT-003 (Solid Biosciences) • RGX-202 (Regenxbio) • INS1201 (Insmed) • BBM-D101 (Belief Biomed) • PF-06939926 (Pfizer) development discontinued	Ph. I/II/III Ph. II and Ph. III Ph. I/II Ph. I/II/III Ph. I/II Ph. I Terminated	France France Abroad (outside France) Abroad (outside France) Abroad (outside France) Abroad (outside France) France
Exon skipping	• NS-089/NCNP-02 (exon 44 skipping) • AOC 1044 (exon 44 skipping) • ENTR-601-44 (exon 44 skipping) • SRP 4045/casimersen (exon 45 skipping) MA (USA) • DS-5141b/renadirsen (exon 45 skipping) development discontinued • NS-050/NCNP-03 (exon 50 skipping) • Eteplirsen (exon 51 skipping) MA (USA) • Vesleteplirsen (exon 51 skipping) development discontinued • PGN-EDO51 (exon 51 skipping) development discontinued • Dyne-251 (exon 51 skipping) • SQY51 (exon 51 skipping) • BMN 351 (exon 51 skipping) • SRP-4053/golodirsen (exon 53 skipping) MA (USA) • NS-065/viltolarsen (exon 53 skipping) MA (Japan, USA) • WVE-N531 (exon 53 skipping)	Ph. II Ph. II Ph. I/II Ph. III Terminated Ph. I/II Ph. III Terminated Terminated Ph. I/II Ph. I/II Ph. I/II Ph. III Ph. I, III and IV Ph. I/II	Abroad (outside France) Abroad (outside France) Abroad (outside France) France Abroad (outside France) Abroad (outside France) France Abroad (outside France) Abroad (outside France) Abroad (outside France) France Abroad (outside France) France Abroad (outside France) Abroad (outside France)
Stop codon readthrough	• Ataluren/Translarna® MA withdrawn/not renewed	STRIDE Registry	France
Cell therapy	• CAP-1002 – cardiac stem cells • DT-DEC01 – chimeric cells	Ph. III Ph. I	Abroad (outside France) Abroad (outside France)
Muscle protection and regeneration			
Reducing inflammation	• Prednisone/prednisolone • Deflazacort MA in the USA, compassionate access in France • Vamorolone (Agamree®) MA (Europe/USA) • Vamorolone (Agamree®) • Canakinumab (ILARIS) • TAS-205 • ATL1102 development discontinued	Prescribed Ph. IV Ph. III (DMD) Ph. II (BMD) Ph. I/II Ph. III Terminated	France Abroad (outside France) Abroad (outside France) Abroad (outside France) Abroad (outside France) Abroad (outside France) Abroad (outside France)
Inhibiting histone deacetylases (HDAC)	• Givinostat (Duvyzat™)/DMD – ambulatory MA (Europe/USA) • Givinostat (Duvyzat™)/DMD – non-ambulatory	Ph. III Ph. III	France France
Protecting myofibrils	• EDG-5506 (sevasemten) in BMD • EDG-5506 (sevasemten) in DMD	Ph. II (BMD) Ph. II (DMD)	France Abroad (outside France)
Obtaining clinical and molecular data			
Natural history studies Registries	• Baseline GNT0004 micro-dystrophin natural history study • BIND study part 1 and 2/cognitive impairment terminated • Registre français des dystrophinopathies [French Dystrophinopathy Registry] • Duchenne Registry	Observational Observational Data collection Data collection	France France France Abroad (outside France)

Producing dystrophin in muscle

Gene therapy

Gene therapy consists of delivering a therapeutic gene (or gene drug) to cells in which a gene is defective or missing using a vector (usually an AAV vector) so that it can make the protein that it codes for.
The delivered gene is called a transgene and is not incorporated into the genome in DMD and BMD therapies.

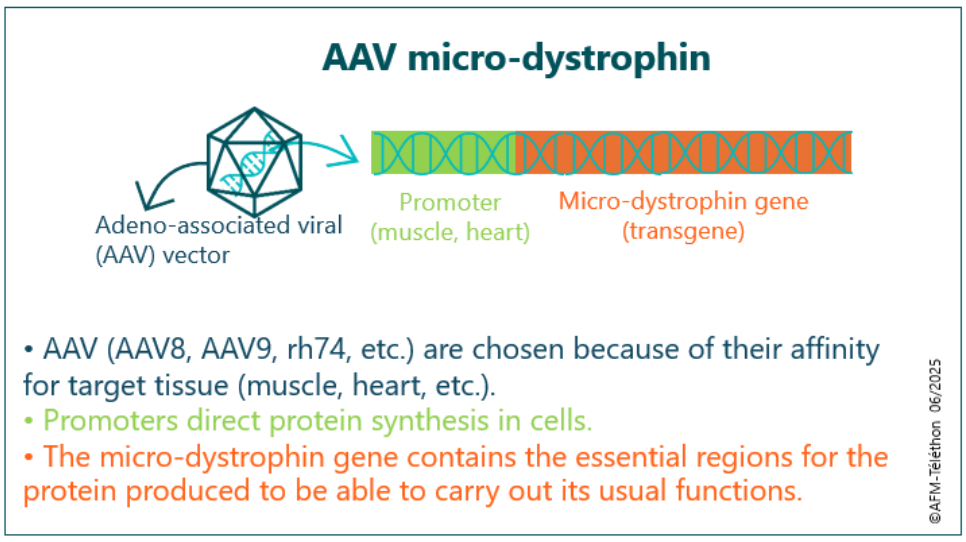


*A **gene** is a "segment" of DNA located in a specific position (locus) on a chromosome. Each gene contains information that constitutes the "manufacturing plan" for a protein.*

*A **vector** is a system used to deliver therapeutic genes into cells in the body so that they can access the nucleus. Once there, the gene can be read (transcribed) to enable its protein to be made.*
A vector can be viral or non-viral (plasmids, lipid-based, etc.).

*A **capsid** is the protein shell of a vector in which therapeutic genes are transported.*

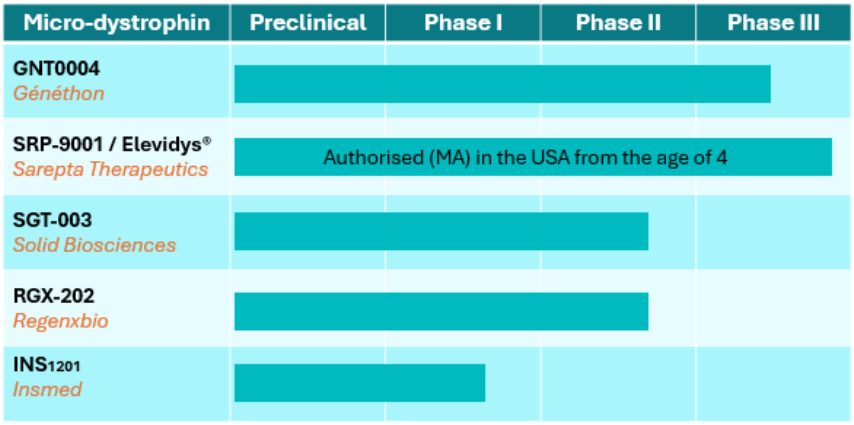
***Dystrophin** contributes to the mechanical strength of muscle cells when they contract. By binding to cell membrane proteins (known as the dystrophin-associated protein complex) and the cell's actin cytoskeleton, it forms a mesh that strengthens muscle cells and anchors them in muscle tissue.*



1 minute pour comprendre : la microdystrophine [1 minute to explain: micro-dystrophin] | AFM-Téléthon

Micro-dystrophins in clinical trials

Several pharmaceutical companies have developed their micro-dystrophin gene therapy products in DMD. Five of them are currently in clinical trials, one of which has already received marketing authorisation. These "similar" products differ from one pharmaceutical company to another (length of the micro-dystrophin gene, type of AAV used for best targeting muscles, less immunogenic capsid, etc.).



Conditions and precautions for micro-dystrophin trials

• Inclusion criteria that exclude patients with certain *DMD* gene deletions from participating in these trials in order to protect them from serious immune reactions. In early trials, side effects in certain patients were attributed to the presence of these deletions in certain regions of the gene.
• The absence of antibodies against the type of AAV (AAV8, AAV9, etc.) used in micro-dystrophin gene therapies is essential as these antibodies interfere with the treatment.
• Immunosuppressive treatment used during the first weeks of the trial to prevent the participants' immune systems from rejecting the product.
• Only one administration of the gene therapy product is possible at present due to the body's subsequent immunity to the new injected substance which occurs naturally.
Bönnemann CG, et al. N Engl J Med. 2023

Why are there always immunologic risks?

• Approximately 10 to 40% of people have antibodies against naturally-occurring AAV, depending on their age and the type of AAV. Patients are always tested to see whether they have antibodies against the AAV being used in a gene therapy technique because if they do, the treatment will be rejected. Pretreatment with drugs such as those used for organ transplants (like imlifidase) are being studied with the aim of reducing anti-AAV antibodies circulating in the blood.
• The capsid of the AAV vector that transports the therapeutic gene is immunogenic, as is the protein produced by it (in this case, micro-dystrophin). Immunosuppressive drugs added to gene therapies help to control these immune reactions, as could modifying AAV vectors, particularly their capsids (an avenue that is being studied).

GNT0004 (Généthon)

Designed by researchers at Généthon (a scientific research laboratory created by AFM-Téléthon) in collaboration with Prof. George Dickson's team at the University of London, GNT0004 combines an AAV8 vector and a gene that codes for a micro-dystrophin.

GNT0004's evaluation in detail

Phase I
Safety/tolerability

Phase II
Dose/effect

Phase III
Efficacy

GNT0004 gene therapy: two inseparable studies

- For all types of DMD gene mutations, except for those involving exons 8 and/or 9
- International programme: France, the United Kingdom and other sites in Europe
- Sponsor: Généthon

1 Natural history study
- **Mandatory before the trial**
- **Recruiting**

- > 200 boys with DMD
- 4 to 9 years old, ambulatory
- No treatment administered
- Minimum clinical follow-up period of 6 months: collection of clinical, imaging and laboratory data (baseline measures for the trial)
- Sites in France: Bordeaux Brest, Bron, Lille, Marseille, Paris Strasbourg

NCT03882827

2 Phase I/II/III trial

Part 1 completed: dose escalation
2 boys dose 1 (1×10^{13} vg/kg)
3 boys dose 2 (3×10^{13} vg/kg)

Part 2 (pivotal trial): summer 2025
> Not yet recruiting
- 64 ambulatory boys (6 to 10 years old) with no antibodies against AAV8, divided into 2 groups of 32 boys
- Placebo-controlled, blinded, crossover design:
  - GNT0004 or placebo: 1 year of follow-up, then
  - Placebo or GNT0004: 1 year of follow-up

Part 3 5 years of follow-up after treatment.

__A crossover study__ allows several treatments to be compared in the same groups of patients. For example, in micro-dystrophin trials, one group will receive the product and another will receive a placebo. Then, after a follow-up period, the group that received the product will receive the placebo and vice versa, followed by another follow-up period.

A __placebo__ is a product whose appearance is identical to a particular drug but does not contain any active substances. In a clinical trial, a placebo is used to measure the true action of a drug.

__The North Star Ambulatory Assessment (NSAA)__ scale measures a patient's ability to perform 17 tasks (including walking, running, jumping, climbing stairs and getting up from the floor) which are given a score of 0, 1, or 2 (unable to perform task to able to perform task independently). The total of these scores, which can range from 0 to 34 (fully-independent function), represents the patient's overall motor function.

Dystrophies musculaires de Duchenne et de Becker : essais et études cliniques en France
[Duchenne and Becker muscular dystrophy: clinical trials and observational studies in France]

Why is this trial being conducted in six to 10 year olds?
Around the age of four to five years old, children with DMD are still developing their motor skills and have not yet lost any. After this period, this development "plateaus", meaning that any changes that may be caused by medication can be observed.

Positive results one year and two years post-injection

Data for the **three patients treated with the second dose** of GNT0004 (3×10^{13} vg/kg) during part 1 of the trial, presented by the pharmaceutical company Généthon at the annual meeting of the American Society of Gene & Cell Therapy (ASGCT) on 16 May 2025, demonstrated:

- **An improvement or stabilisation** in motor function.

One year after treatment, their NSAA scores were 4.7 points higher on average than those of the group of 34 untreated patients from the natural history study - a significant difference.

Two years after treatment, this difference reached +8.8 points on average for two of the three patients compared to the average obtained by a group of 17 untreated patients from the natural history study.

- **A significant reduction in CK levels in the blood.**

The average reduction was 68% one year after treatment and 75% at 18 months post-treatment. This reduction lasted for up to 24 months in the first two patients treated with the effective dose.

- **A favourable safety profile of the product** with no serious side effects.

These results were obtained with a dose lower than those used in other micro-dystrophin gene therapies currently being developed. The aim of the pivotal study is to evaluate these effects in a larger number of patients with the hope of confirming them.

AFM-Téléthon press release 19 May 2025

How do we know whether the observed changes are significant?
In collaboration with AFM-Téléthon, a group of international experts in DMD analysed the functional and motor trajectories of patients. They gathered data and observations on 1,000 ambulatory patients aged four to 18 years old receiving corticosteroid therapy from clinical trial placebo groups, natural history studies and real-world settings.
Minimal detectable change (MDC) thresholds were defined with a confidence interval set at 80%:
• 2.8 points for the NSAA scale,
• 1.3 seconds for the four-stair climb (4SC) time,
• 0.36 stairs/second for the 4SC velocity,
• 36.3 meters for the six-minute walk test (6MWT).
The authors deems that any improvements or changes observed above these thresholds would be due to treatment. They constitute valuable benchmarks for interpreting clinical trial results.
Muntoni F, et al. PLoS One. 2024

Changes in motor function and walking ability *are evaluated in clinical trials and real-life settings using measures such as the six-minute walk test (6MWT), four-stair climb (4SC) time, 4SC velocity and the NSAA scale.*

SRP-9001/Elevidys® (Sarepta) - MA since 2023

Developed by the pharmaceutical company Sarepta Therapeutics, SRP-9001 (delandistrogene moxeparvovec) is made up of an rAAVrh74 vector (a serotype very similar to AAV8) that targets skeletal and cardiac muscle cells.

Milestones achieved for SRP-9001 (Elevidys®)
▪ MA in 2023 in the United States extended in June 2024 for boys with DMD over the age of four (except for those with deletions in exons 8 and/or 9 in the *DMD* gene). Elevidys® has been approved in nine other countries.
▪ **In Europe**, a marketing authorisation application (MAA) is currently being reviewed by the EMA for ambulatory boys aged three to seven years old (submitted by the pharmaceutical company Roche which is developing the product outside the United States in collaboration with Sarepta).
▪ In the EMBARK trial, efficacy results were significant two years after treatment (+2.88 points on average in the NSAA scores of boys aged four to under eight years old compared to an untreated external group).
▪ A recent analysis of the side effects and limitations of Elevidys®, as well as its effect on function, in four out of six available trials indicated the need to collect further efficacy data.
▪ Following the death of a second non-ambulatory adolescent treated with Elevidys® (from acute liver failure), trials in Europe were temporarily halted, including ENVOL (one site in France since 2024) and ENVISION (ongoing internationally, in preparation in France), as was all dosing of non-ambulatory patients.
▪ The benefit/risk ratio remains positive in ambulatory patients.
Mendell JR. et al. Sarepta Therapeutics, 2025 ASGCT Annual Meeting
Oskoui M. et al. Neurology. 2025 — *Mendell JR et al. Nat Med. 2025*
AFM-Téléthon news, 26 June 2024 [article in French] — *Roche press release 15 June 2025*

Marketing authorisation *(MA) enables a new drug to be sold. It is granted in France by the ANSM (Agence nationale de sécurité du médicament et des produits de santé [French medicines agency]) or, at a European level, by the European Commission, after consulting the European Medicines Agency. To be granted marketing authorisation, the pharmaceutical company must provide scientific data from the development phases, in particular from clinical trials. The decision is made based on safety, efficacy and quality criteria.*

• Phase II ENVOL trial: **temporarily halted.** One site in France (Hôpital Necker-Enfants Malades [Necker Children's Hospital]) (sponsor: Roche).

Open-label ENVOL trial

France and abroad	21 Under 4 years old	Paused on 15/06/2025	Nov 2023 – May 2033 5 years of follow-up after treatment

NCT06128564

Phase II
Dose/effect

Phase III
Efficacy

• Phase III ENVISION trial**: temporarily halted**

Placebo-controlled ENVISION trial (ambulatory/non-ambulatory)

Abroad (outside France) | **148 (over 8 years old)** | **Paused on 15/06/2025** | **May 2023 – June 2028 3 years of follow-up after treatment**

NCT05881408

Phase III
Efficacy

• Phase III EXPEDITION study: five-year follow-up of 400 patients of all ages previously treated with SRP-9001 in other trials (trial completion: 2030) (NCT05967351).

Imlifidase in trials for immunomodulation

Imlifidase (Idefirix®) is a drug that contains a bacterial enzyme called IdeS which destroys antibodies circulating in the blood. It is used to desensitise highly sensitised patients awaiting kidney transplantation.

In studies conducted by Giuseppe Ronzitti's team at Généthon on animal models immunised against AAV, IdeS degrades circulating antibodies and therefore enables AAV vectors to be injected without neutralising the treatment. It was evaluated as a pretreatment in gene therapy trials using AAV in patients with pre-formed antibodies to AAV (DMD, Crigler-Najjar syndrome).

Généthon press release 3 December 2024

Phase I
Safety/tolerability

• A phase I study conducted in six patients aged four to nine years old in Spain is evaluating imlifidase's ability to modulate the immune response to micro-dystrophin gene therapy. This drug is administered before SRP-9001 in patients who have already developed antibodies against the rAAVrh74 virus (a micro-dystrophin gene transporter) (NCT06241950).

SGT-003 (Solid Biosciences)

The pharmaceutical company Solid Biosciences developed SGT-003 after SGT-001 failed to provide proof of its efficacy. **SGT-003** uses an AAV-SLB101 vector that better targets muscle and cardiac cells but avoids the liver thanks to an optimised capsid. The micro-dystrophin that it produces contains the binding domain for the submembranous nNOS (neuronal nitric oxide synthase) protein which is essential for effective muscle vascularisation. SGT-003 trials exclude patients with deletion mutations in exons 1 to 11 or 42 to 45 in the *DMD* gene.

SGT-003 evaluated in the INSPIRE DUCHENNE trial

The first part of this trial provided results for three out of the six patients included three months after treatment:

- micro-dystrophin detected in 78% of muscle fibres on average with nNOS co-localisation in half of them, and average micro-dystrophin levels reached 110% of normal;
- reduction in biomarkers of muscle breakdown (e.g. CK);
- SGT-003 well tolerated in the six patients treated;
- five-times greater transduction (the process by which genetic material is transferred into a cell using a viral vector) in muscle with less product compared to first-generation therapies (e.g. Elevidys®);
- excellent transduction in cardiac muscle.

Solid Biosciences, SGT-003 INSPIRE DUCHENNE DATA UPDATE, 2025 Feb.

Open-label trial of SGT-003 (INSPIRE DUCHENNE)

Phase I
Safety/tolerability

Phase II
Dose/effect

United States and Canada	43 4 to < 12 years old	Recruiting	May 2024 - May 2031 5 years of follow-up

NCT06138639

RGX-202 (Regenxbio)

Developed by the pharmaceutical company Regenxbio, RGX-202 combines the NAV® AAV8 vector, a micro-dystrophin containing the extended C-Terminal domain found in naturally occurring dystrophin, and Spc5-12, a skeletal and cardiac muscle-specific promoter. RGX-202 has been shown to be effective in mdx mouse models of DMD.

Three RGX-202 studies are currently taking place. Patients with mutations in exons 12 to 17 are excluded from these trials.

• The AFFINITY BEYOND observational study is evaluating the presence of anti-AAV8 antibodies in 200 DMD patients under the age of 12 and identifying potential participants for the AFFINITY DUCHENNE trial (study completion: 2026) (NCT05683379).

• The AFFINITY DUCHENNE trial (phase II/III) is evaluating the efficacy, safety and tolerability of RGX-202. It is being conducted in three parts: ❶ two doses are evaluated first ❷ the effective dose is evaluated in 30 patients (pivotal phase) ❸ 30 more patients are treated.

*A **pivotal trial** is usually a phase III, randomised, controlled, double-blind clinical trial designed to provide data required by a regulatory authority to make a decision on marketing authorisation.*

Open-label trial of RGX-202 (AFFINITY DUCHENNE)

Phase I
Safety/tolerability

Phase II
Dose/effect

Phase III
Efficacy

United States and Canada	65 (over 1 year old)	Recruiting	Jan 2023 – Aug 2028 2 years of follow-up

NCT05693142

• A long-term RGX-202 study is evaluating patients previously treated with RGX-202 over five years (study completion: 2029) (NCT06491927).

Interim results for RGX-202

▪ RGX-202 was well tolerated in 12 patients (one to 11 years old) during the first part of the AFFINITY DUCHENNE trial.

▪ Results showed robust expression, successful transduction, and sarcolemmal localisation of RGX-202 micro-dystrophin three months after administration for both doses evaluated.

▪ Clinically meaningful improvements in functional outcomes were observed, particularly with the second dose, with an average 7.3-point improvement in NSAA scores for two of the patients treated compared to untreated external controls.

Regenxbio, Interim clinical data, 9 April 2025

INS1201 (Insmed) - now in clinical trials NEW

INS1201, developed by the pharmaceutical company Insmed, is made up of an AAV9 vector and a micro-dystrophin gene. It has been shown to be effective in preclinical trials conducted in mdx mouse models of DMD, with a durable expression of micro-dystrophin and distribution in skeletal muscle and the heart.

*An **intrathecal injection** is a route of administration that involves injecting a drug into the cerebrospinal fluid. In order to do this, a needle is inserted between the vertebrae of the spine (which protects the spinal cord).*

Phase I
Safety/tolerability

A phase I trial evaluating INS1201 has just started

It will include boys with DMD aged two to five years old, and will exclude those with mutations in exons 1 to 17 and/or 59 to 71 in the *DMD* gene. The therapy is administered via **intrathecal injection** and not intravenously.

Open-label trial of INS1201 (ASCEND)

United States	12 (2 to < 5 years old)	Recruiting	May 2025 – March 2028 2 years of follow-up

NCT06817382

ASGCT 28th Annual Meeting Abstracts, abstracts 1080 & 1352. 28 April 2025

BBM-D101 - utrophin and dystrophin gene therapy

Developed by the pharmaceutical company Belief Biomed, this gene therapy product includes an AAV vector with an optimised capsid to better target muscles and reduce product doses. It transports a minigene that contains regions of utrophin and dystrophin (iAAV9.6/shCK.mini-UDYS.spolyA).

▪ In July 2024, the first phase I, open-label clinical trial started in China in six participants with DMD aged four to eight years old who were treated with a single injection of BBM-D101 and monitored for five years (NCT06641895).

Utrophin - a protein 80% identical to dystrophin

Utrophin is produced in the human body during the formation of muscles. In mature muscle cells, utrophin hands over to dystrophin and its production is suppressed. However, a small amount of utrophin is still produced in muscles affected by dystrophy (research shows that its absence worsens the disease) which compensates for the absence of dystrophin. Research projects are attempting to evaluate molecules that activate it.

PF-06939926 (Pfizer) - development discontinued

The pharmaceutical company Pfizer was developing PF-06939926 (fordadistrogene movaparvovec), a muscle-targeted AAV9.CK.mini-dystrophin gene therapy product.

***The North Star Ambulatory Assessment (NSAA)** scale measures a patient's ability to perform 17 tasks (including walking, running, jumping, climbing stairs and getting up from the floor) which are given a score of 0, 1, or 2 (unable to perform task to able to perform task independently). The total of these scores, which can range from 0 to 34 (fully-independent function), represents the patient's overall motor function.*

Milestones achieved for PF-06939926

▪ The product was evaluated in the international phase III CIFFREO trial in boys aged four to seven and two sites in France included participants (NCT03362502).

▪ **In June 2024,** the pharmaceutical company Pfizer reported that PF-06939926 had not met its primary (improvement in motor function assessed using the NSAA scale) or secondary endpoints (10-metre run/walk velocity, time to rise from floor velocity, etc.) at one year after treatment compared to a placebo. The safety profile was satisfactory.

▪ **On 30 July 2024,** following these results, the pharmaceutical company announced that it would discontinue its development of PF-06939926. The boys treated in the CIFFREO trial will continue to be monitored in the long term by the investigator site.

Pfizer press release 12 June 2024
Cureduchenne, Pfizer press release 30 July 2024

Micro-dystrophin - challenges and ways to improve

An article published by a team at Généthon reviewed the progress, challenges and improvements made in the micro-dystrophin approach, citing in particular:

- the improvement of AAV vectors and their capsids to facilitate the delivery of gene therapy products to target tissue (skeletal muscle, heart) while avoiding the liver in order to limit toxicity;
- the development of AAV gene therapy strategies to obtain full-length dystrophin in cells using different techniques such as DNA trans-splicing, homologous recombination and protein trans-splicing;
- the need to better understand certain mechanisms in DMD in order to be able to target them with treatments combined with gene therapy.

Jaber A. et al. Med Sci (Paris). 2024 Nov;40 Hors-série n°1 [article in French]

Preclinical studies - avenues to pursue

Nearly full-length dystrophin reconstituted using inteins

Two different teams (one of which was supported by AFM-Téléthon) managed to obtain full-length dystrophin by administering three different fragments of the dystrophin gene. Three fragments of the *DMD* gene, into which sequences coding for inteins had been inserted, were each packaged in a muscle-targeted AAV vector and administered in mdx mice. Intein sequences are able to cut themselves during protein formation, allowing the remaining fragments on either side to join back up. The production of nearly full-length dystrophin in skeletal and cardiac muscle has been achieved in mice (young and old) whose muscle function improved.

Tasfaout H. et al. Nature. 2024 *Zhou Y. et al. Nat Commun. 2024*

Using genome editing to produce slightly truncated dystrophin

The genome editing company Precision Biosciences developed PBGENE-DMD, a product composed of an ARCUS nuclease (designed to cut and remove exons 45 to 55 from the *DMD* gene - a "hotspot" for *DMD* gene mutations) packaged in an AAV vector. The administration of PBGENE-DMD in mouse models of DMD led to dystrophin expression in muscles, including in satellite cells (muscle stem cells). Their force increased and stabilised after six months (in contrast to untreated mice).

ASGCT 28th Annual Meeting Abstracts, abstract 1129, 28 April 2025

Using genome editing to overexpress utrophin

Chinese researchers developed a gene therapy product using a genome editing approach for the *UTR* gene combined with a muscle-specific viral vector called Myo-AAV to increase the production of utrophin. The administration of MyoAAV-UA in animal models led to robust and durable utrophin expression with no particular toxicity observed (including in primates), and significant improvements in function. This is an interesting approach which can be applied regardless of the type of *DMD* gene mutation.

Wu R. et al. Nat Commun. 2025

*The term "**genome editing**" refers to a set of techniques used to modify the DNA sequences that make up the genome. They use molecular tools that precisely target the chosen sequence (using small guide RNA) and modify it using Cas enzymes (Cas9, Cas12, etc.) which are capable of cutting DNA in order to remove a sequence or enable it to be modified.*

www.afm-telethon.fr/fr/termes/crisprcas9 [page in French]

Exon skipping

Targeting deletions in the dystrophin gene (*DMD*)

Antisense oligonucleotides are small sequences of RNA (or DNA) made in a laboratory that, once delivered to a cell, restore the expression of a gene (ability to make its protein). Targeted mutations are generally deletions of one or several exons. This means that part of the gene is missing, disrupting the readability of the message it carries. This makes it impossible for the corresponding protein to be made.

With 79 exons, the *DMD* gene is particularly susceptible to deletions

- Deletions account for 70% of all mutations in the *DMD* gene
- 11% of them affect more than one exon
- 60% of deletions occur between exons 45 and 55, the "hotspot" region of the *DMD* gene
- The majority of antisense oligonucleotides target this region
- Skipping either exon 44, 45, 51 or 53 is applicable to nearly 35% of patients

Skipping a specific exon to restore the gene's reading frame

Antisense oligonucleotides get to work during the formation and maturation (splicing) of mRNA from a gene. During this maturation process, they bind to a specific exon (located close to the causative deletion) in order to remove it (hence the name "exon skipping") and restore a readable message which can then be translated into the gene's protein - a smaller, supposedly active dystrophin.

Messenger RNA (mRNA) *is a copy of a gene's DNA that has retained only the exons. It is a molecular intermediary between a gene and its protein, the structure of which dictates the amino acid sequence of the protein.*

Skipped exon	*DMD* gene deletions potentially treated
7	2-6, 8-11, 8-17, 8-43, 8-45
8	4-7, 5-7, 6-7, 3-7
17	12-16, 18, 18-20, 18-22, 18-25, 18-27, 18-29, 18-33, 18-36, 18-38, 18-41, 18-44
44	10-43, 19-43, 30-43, 35-43, 36-43, 40-43, 42-43, 45, 45-54
45	12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, 46-55
50	51, 51-53, 51-55
51	45-50, 47-50, 48-50, 49-50, 50, 52
52	53, 53-55, 53-57, 53-59, 53-60
53	10-52, 45-52, 46-52, 47-52, 48-52, 49-52, 50-52, 52
55	47-54, 48-54, 49-54, 50-54, 52-54, 54, 56, 56-62

Duchenne.com: Exon Skipping

Antisense oligonucleotides seeking improvement

- **PMO** (phosphorodiamidate morpholino oligomers) or "morpholinos" struggle to reach cell nuclei and therefore require frequent dosing (e.g. eteplirsen, casimersen, golodirsen, viltolarsen).
- **Conjugated PMO** work much better due to their conjugated compounds, which could be:
  - a peptide (to make a peptide-conjugated phosphorodiamidate morpholino oligomer or "**PPMO**") (e.g. SRP-5051, PGN-EDO51).
  - a fragment antibody (Fab) that binds to TfR1 (transferrin receptor 1) (e.g. DYNE-251, AOC 1044).
  - an Endosomal Escape Vehicle or "EEV" (e.g. Entr-601-44, Entr-601-45).

• **Tricyclo-DNA antisense oligonucleotides** (e.g. SQY51) have a higher affinity for mRNA molecules and better resistance to nuclear enzymes.
• **Stereopures** are less toxic and more effective (e.g. WVE-N531).
• **AAV-U7** enable continuous oligonucleotide production in cells using nuclear RNA delivered by an AAV (e.g. scAAV9.U7.ACCA).
Matsuo M. Int J Mol Sci. 2025
Haque U.S. et al. Curr Res Toxicol. 2024

Fourteen antisense oligonucleotides

Skipped exon	Antisense oligonucleotide	Clinical trial phase					Authorised (MA)
		I	I/II	II	III	IV	
44	NS-089/NCNP-02 AOC 1044 NEW ENTR-601-44						
45	Casimersen (Amondys 45®) NEW ENTR-601-45						USA - 2021
50	NS-050/NCNP-03 NEW GEN6050X						
51	Eteplirsen (Exondys 51®) SQY51 DYNE-251 BMN 351						USA - 2016
53	Golodirsen (Vyondys 53®) Viltolarsen (Viltepso®) WVE-N531						USA - 2020 Japan/USA - 2020

Phase I
Safety/tolerability

Phase II
Dose/effect

Phase III
Efficacy

Phase IV
Pharmacovigilance

Exon 44 skipping - three antisense oligonucleotides in trials

1 NS-089/NCNP-02 (brogidirsen) - hoping to be more effective than its predecessor

Developed by the Japanese pharmaceutical company Shinyaku Co. Ltd, the National Center of Neurology and Psychiatry in Japan and NS Pharma in the United States, this antisense oligonucleotide is hoped to be more effective than previous ones from the same pharmaceutical company (viltolarsen) thanks to the addition of two linked sequences that target two binding sites within exon 44.

Two clinical trials currently taking place

Phase II
Dose/effect

▪ A phase II, open-label extension in six patients aged four to 17 years old previously treated in a phase I/II trial (completed) monitored for five years in Japan (NCT05135663).
▪ A phase II, open-label trial in 20 ambulatory patients aged four to 14 years old monitored for one year in the United States (NCT05996003).

Results of the phase I/II trial

Six patients (four to 13 years old) were treated with different doses of brogidirsen once a week for six months. Their evaluations at the end of treatment showed:
• dose-dependent dystrophin production in muscle (24.5% of normal dystrophin levels achieved with 80 mg/kg of brogidirsen);
• favourable safety and tolerability and a decrease in serum biomarkers of muscle breakdown.
Komaki H. et al. Cell Rep Med. 2025

❷ AOC 1044 (del-zota) - successful delivery into muscle cells

AOC 1044 is a PMO conjugated to an antibody that binds to TfR1 (transferrin receptor 1) on the surface of muscle cells to facilitate its delivery. This means that doses of AOC 1044 (every six to eight weeks) are spaced further apart than those of an unconjugated PMO. It targets skeletal muscle and the heart.

Phase I
Safety/tolerability

Phase II
Dose/effect

Well tolerated and good for muscle

The initial findings from part two of the American phase I/II EXPLORE44 trial (NCT05670730) in DMD patients aged seven to 55 years old (ambulatory or non-ambulatory) were announced by the pharmaceutical company Avidity Biosciences which is developing AOC 1044. One month after receiving the third dose, results were assessed from seven patients receiving 5 mg/kg every six weeks, 10 patients receiving 10 mg/kg every eight weeks, and six placebo patients.

- AOC 1044 was well tolerated and safe at both doses evaluated.
- Exon 44 skipping restored 25% to 58% of normal dystrophin levels.
- Creatine kinase (CK) levels decreased by more than 80%.

The functional results are expected to be released at the end of 2025.
Avidity Biosciences, Del-zota EXPLORE44 ® Phase 1/2 Topline Data, 17 March 2025

▪ The phase II, open-label EXPLORE44OLE trial is currently taking place over two years in 39 participants from the EXPLORE44 trial (seven to 55 years old, ambulatory or non-ambulatory), with intravenous administration of AOC 1044 at the 5 mg/kg dose every six weeks (NCT06244082).

❸ ENTR-601-44 - facilitating endosomal escape NEW

*An **endosome** is a small spherical structure (a vesicle) that forms by the invagination (folding inwards) of a cell's membrane in order to internalise molecules and transport them to the cytoplasm*

Using its Endosomal Escape Vehicle (EEV™) platform, the pharmaceutical company Entrada Therapeutics identified compounds that help release antisense oligonucleotides from endosomes. ENTR-601-44 contains an EEV and can only be administered once every six weeks.

How does it work?

When they reach the surface of cells, antisense oligonucleotides intended for exon skipping are internalised by endosomes which transport them to the nucleus where they are released so that they can perform their intended actions. However, some remain trapped in the endosomes, limiting the amount of active product that reaches the nucleus. Conjugated peptides called oligonucleotide-enhancing compounds help release them.
Li X. et al. Mol Ther Nucleic Acids. 2023 *Bizot F. et al. Cells. 2023*

Positive results in healthy volunteers

The results of a phase I trial in the United Kingdom that evaluated several doses of ENTR-601-44 (0.75 mg/kg to 6 mg/kg every six weeks) compared to a placebo in 32 healthy volunteers showed that ENTR-601-44 was well tolerated and resulted in exon 44 skipping in muscle cells.

Phase I
Safety/tolerability

Phase II
Dose/effect

▪ A phase I/II trial of ENTR-601-44 is in the works. It has been approved in the United Kingdom and the United States for DMD patients who are exon 44 skipping amenable and is expected to start in the coming months.

Other products: Entrada Therapeutics is developing other products similar to ENTR-601-44 intended to skip other exons (45, 50, 51). A trial of ENTR-601-45 is expected to start in Europe soon.

Entrada Therapeutics, Corporate Presentation, June 2025

Exon 45 skipping - one product authorised, still in clinical trials

Casimersen (Amondys 45®/SRP-4045) authorised

This PMO was developed by Sarepta Therapeutics. It was authorised in the United States for DMD in 2021 and is still being evaluated in real life.

Phase III
Efficacy

▪ The ESSENCE trial, which is evaluating casimersen in boys aged six to 13 years old, is still underway and is due to be completed at the end of 2025 (NCT02500381).

More information on the ESSENCE trial [page in French]

Exon 50 skipping - one antisense oligonucleotide in trials

NS-050/NCNP-03 NEW

This antisense oligonucleotide is one of several exon skipping candidates from the pharmaceutical company NS Pharma, an American subsidiary of the Japanese group Nippon Shinyaku, which is also developing viltolarsen (exon 53 skipping) and NS-089/NCNP-02 (exon 44 skipping).

Phase I
Safety/tolerability

Phase II
Dose/effect

▪ A phase I/II clinical trial (Meteor 50) in 20 boys aged four to 14 years old with DMD amenable to exon 50 skipping started in September 2024 in the United States and Japan (NCT06053814).

Exon 51 skipping - four products in trials (one authorised)

1 Eteplirsen (Exondys 51®)

This PMO was developed by Sarepta Therapeutics and was approved in the United States in 2016. It is administered intravenously once a week.

▪ The MIS51ON trial is evaluating high doses of eteplirsen (100 then 200 mg/kg/week) compared to the usual dose (30 mg/kg/week).

Phase III
Efficacy

Trial of high doses of eteplirsen in DMD (MIS51ON)

France and abroad	160 (4 to 13 years old)	Not recruiting	July 2020 – Oct 2026 3 years of follow-up

NCT03992430

More information on the MIS51ON trial [page in French]

Positive outcomes perceived by carers of children treated with eteplirsen

An American study examined the views of 15 carers (12 mothers, two fathers and one auntie) of DMD patients aged seven to 15 years old who had been treated with eteplirsen for three to 24 months (nine ambulatory/six non-ambulatory). The carers were interviewed and asked questions about their son or nephew's physical functioning, activities of daily living and quality of life. The majority of the carers perceived improvements in or a maintenance of their physical functioning (walking, running, climbing stairs, upper limb function and fine-motor

movements), and roughly half of them witnessed less fatigue, muscle weakness and pain - effects which they perceived as positive.
Iff J. et al. Adv Ther. 2024

2 SQY51 - a tricyclo-DNA antisense oligonucleotide

Developed by the French pharmaceutical company SQY Therapeutics, the tricyclo-DNA antisense oligonucleotide SQY51 has a higher affinity for targeted mRNA molecules and better resistance to nuclear enzymes.

The AVANCE1 trial continues

Phase I
Safety/tolerability

Phase II
Dose/effect

Open-label trial of SQY51 in DMD (AVANCE1)

France (Garches) | **12 (over 6 years old)** | **Not recruiting** | **April 2023 – Feb 2025 1 year of follow-up**

NCT05753462

More information on the SQY51 trial [page in French]

This phase I/II, single-site trial (Hôpital Raymond-Poincaré [Raymond-Poincaré Hospital], Garches, France) is evaluating the safety and tolerability of SQY51, its effect on function and the amount of dystrophin produced in muscle.

First "dose escalation" part completed

The first part of this trial lasted 13 weeks and evaluated escalating doses of SQY51 (2, 4, 6, 10, 16 and 25 mg/kg) given in six intravenous infusions. The second part of this trial, which is currently underway, is expected to consolidate safety and pharmacokinetic data for SQY51. Three doses are being evaluated (10, 16 and 25 mg/kg) in three patient cohorts. The product is administered once a week for four weeks followed by a four-week break, all of which is repeated four times.
SQY Therapeutics press release 4 March 2025 [page in French]

3 DYNE-251 - a higher affinity for muscle cells

Developed by the pharmaceutical company Dyne Therapeutics, DYNE-251 is a PMO conjugated to an antibody that binds to TfR1 (transferrin receptor 1).

One phase I/II trial currently underway

This trial includes a double-blind, placebo-controlled, dose escalation part lasting six months with administration every four weeks and a long-term follow-up period.

Phase I
Safety/tolerability

Phase II
Dose/effect

Double-blind DMD trial (DELIVER)

International (sites in Europe) | **86 (4 to 16 years old) (amb/non-amb)** | **Not recruiting** | **Aug 2022 – Nov 2029 3 years of follow-up**

NCT05524883

Positive safety, tolerability and initial functional results

• The product is well tolerated (some patients have been treated for more than two years);
• Average dystrophin expression reached 3.72% of normal levels after six months of treatment (20 mg/kg) in six patients;
• Functional outcome measures (SV95C, NSAA, etc.) after 18 months of treatment (20 mg/kg) seemed to improve (full results expected at the end of 2025).

Phan H. et al. MDA Conference, 16-19 March 2025
Dyne-sponsored symposium, MDA Conference, 16-19 March 2025

__SV95C__ (stride velocity 95th centile) is a digital ambulation measure obtained by using an electronic device worn on the ankle.

__The North Star Ambulatory Assessment (NSAA)__ scale measures a patient's ability to perform 17 tasks (including walking, running, jumping, climbing stairs and getting up from the floor) which are given a score of 0, 1, or 2 (unable to perform task to able to perform task independently). The total of these scores, which can range

4 BMN 351 - a third-generation antisense oligonucleotide

The pharmaceutical company BioMarin Pharmaceutical, who was there at the very beginning of exon skipping research, developed BMN 351 - a new generation of antisense oligonucleotide.

▪ A phase I/II trial in Europe has been evaluating it since January 2024 in 18 ambulatory boys aged four to 10 years old with DMD amenable to exon 51 skipping. This trial includes an initial dose escalation part in order to determine the effective dose and the ideal spacing between two injections (NCT06280209).

Exon 53 skipping - three products (two authorised)

1 Golodirsen (Vyondys 53®/SRP-4053)

SRP-4053, a PMO developed by Sarepta Therapeutics, has only been authorised in the United States (since 2019). It is administered intravenously once a week.

▪ The ESSENCE trial (which is evaluating it) is still underway.

Trial of SRP-4045 and SRP-4053 in DMD (ESSENCE)

Phase III
Efficacy

France and abroad	228 (6 to 13 years old)	Not recruiting	Sept 2016 – Oct 2025 3 years of follow-up

NCT02500381

More information on the ESSENCE trial [page in French]

2 Viltolarsen (Viltepso®/NS-065/NCNP-01)

NS-065/NCNP-01 is a PMO developed by the Japanese pharmaceutical company Shinyaku Co. Ltd, NS Pharma and the National Center of Neurology and Psychiatry which has been optimised so that it is able to target pre-mRNA more effectively. It was authorised in Japan and the United States in 2020 (not in Europe).

▪ A post-MA access programme for viltolarsen/Viltepso® (weekly infusions) is taking place in the United States to provide access to patients aged three to 12 years old (NCT04337112).

A __placebo__ is a product whose appearance is identical to a particular drug but does not contain any active substances. In a clinical trial, a placebo is used to measure the true action of a drug by comparing the effects of the drug (which contains the active substance) to those of the placebo.

Positive results in terms of:

▪ **Pulmonary function.** The results of the Galactica53 trial (NCT04956289) of viltolarsen involving 20 patients over the age of eight years old (10 ambulatory and 10 non-ambulatory) treated for one year showed:

• an improvement or stabilisation in pulmonary function in the majority of these patients compared to untreated patients outside the trial;
• a forced vital capacity of over 50% in nine out of the 10 ambulatory patients and in six of the 10 non-ambulatory patients. Peak cough flow values remained at 160 L/min or higher for seven of the non-ambulatory patients and six of the ambulatory patients.

▪ **Motor function.** A retrospective study of five patients aged six to 19 years old treated with viltolarsen in real life for at least three years showed that uninterrupted treatment administered once a week maintained motor function (one of these patients did show a decline in motor function, however, it was very slow). One of the patients whose treatment was intermittent and eight out of nine untreated external controls experienced a decline in their motor function.

Harper AD. Et al. Sci Rep. 2024 *Funato M. et al. Brain Dev. 2025*

Phase III Efficacy
Phase IV Pharmacovigilance

Viltolarsen trials still taking place:
• A phase IV trial in the United States and Canada (VILT-502) (trial completion: October 2032) (NCT04687020);
• An international, phase III trial (RACER53-X) for DMD patients of all ages (trial completion: November 2025) (NCT04760062).

❸ WVE-N531 - a stereopure

Developed by Wave Life Sciences, WVE-N531 is an exon 53 skipping therapy. Its "stereopure" chemical structure should limit its toxicity and improve its efficacy.

▪ A phase I/II trial with two parts is currently taking place.

Phase I Safety/tolerability
Phase II Dose/effect

Open-label trial of WVE-N531 in DMD (FORWARD-53)

Abroad (outside France)	11 (5 to 18 years old)	Not recruiting	Sept 2021 – Oct 2026 8 weeks of follow-up

NCT04906460

Positive results from the FORWARD-53 trial after one year

Eleven participants aged five to 11 years old (only one non-ambulatory) were treated with WVE-N531 every two weeks for one year. The product was well tolerated and no serious adverse events were reported.
• Muscle biopsies showed that dystrophin expression stabilised between six months and one year and averaged 7.8% of normal levels.
• Inflammation and necrosis scores were reduced by half. Muscle biomarkers like CK reached values comparable to those seen with stable corticosteroid therapy.
• Initial functional outcome measures indicated an improvement of 3.8 seconds in time-to-rise compared to untreated external controls.

Wave Life Sciences press release 26 March 2025 and 24 September 2024

Products whose development has been discontinued

Renadirsen (DS-5141b) - exon 45 skipping

▪ A phase II trial evaluating renadirsen in seven DMD patients (over 5 years old) in Japan was terminated at the start of 2025, signalling the end of the product's development by Daiichi Sankyo.

jRCT2080225225, Japan Registry of Clinical Trials

PGN-EDO51 - exon 51 skipping

Evaluated in the phase II CONNECT1-EDO51 trial (NCT06079736), PGN-EDO51 did not achieve sufficient dystrophin levels in the patients treated. The pharmaceutical company PepGen announced that it was discontinuing its development of PGN-EDO51 and its DMD-related programmes.

PepGen press release 28 May 2025

Vesleteplirsen (SRP-5051) - exon 51 skipping

This improved version of eteplirsen, developed by Sarepta Therapeutics, could be injected once a month instead of once a week. In the MOMENTUM trial (NCT04004065), it brought about dystrophin expression but its side effects (low blood magnesium levels, kidney problems) led to Sarepta discontinuing its development.

Sarepta Therapeutics press release 6 November 2024

Preclinical studies - exon skipping using "single-cut" genome editing

A Chinese team developed a single-cut gene therapy product using Cas12iMax technology (similar to CRISPR/Cas9) and a muscle-targeting MyoAAV vector. It targets exon 51 in the *DMD* gene and cuts out the part that shifts the gene's reading frame. One year and a half after it was injected in a 17-month-old rhesus monkey model of DMD, dystrophin expression was restored and muscle and motor function improved. No safety concerns were reported. These positive results observed in a single animal demonstrate the feasibility of this genome editing-based gene therapy. Large-scale studies nevertheless remain essential if it is to be evaluated in humans.

Bai R et al. Cell Rep Med. 2025

CRISPR/Cas systems - tools that are becoming more diverse

This approach uses molecular tools that precisely target a region of a gene's DNA using small guide RNA in order to modify it (remove a piece of DNA, correct a mutation, modify the reading frame of the gene, change a splicing site in order to induce exon skipping). These tools have been fine-tuned to ensure that they target the intended areas of DNA and do not modify other areas by mistake. In addition, more efficient vectors for delivering these molecules to the body (such as nanoparticles) are available.

Messenger RNA (mRNA) *is a copy of a gene's DNA from which the protein is made. The mRNA's nucleotide sequence dictates the protein's amino acid sequence, composition and structure.*

Stop codon readthrough - the end of ataluren (Translarna®)

Just under 13% of DMD and BMD patients have "nonsense" mutations in their *DMD* genes that introduce a premature "stop codon" into mRNA which stops normal dystrophin from being made.
"Readthrough agents" encourage cells to ignore these stop codons so that a functional protein can be made.

Ataluren (Translarna®) is a readthrough agent developed by the pharmaceutical company PTC Therapeutics to enable dystrophin production in muscle in DMD.
Ataluren was granted conditional marketing authorisation in Europe in July 2014 based on the initial results of clinical trials that were evaluating it. This authorisation was provisional pending further, more convincing efficacy data on whether ataluren preserved the ability to walk and an established benefit/risk ratio. Unfortunately, results obtained since its authorisation have not been able to confirm its efficacy, despite the hopes of some trials.

• **On 28 March 2025,** the European Commission announced the definitive withdrawal of marketing authorisation for Translarna® in Europe, leaving it up to Member States to decide for themselves whether they wanted to allow a temporary continuation of treatment.
• **On 17 June 2025 in France,** following advice from the ANSM, the ministers in charge of health and social security consequently decided to end the French social security system's exceptional coverage of this treatment.
Translarna is therefore no longer available in France.

ANSM, Arrêt de mise à disposition suite au non-renouvellement de l'AMM conditionnelle européenne [Translarna no longer available following non-renewal of conditional marketing authorisation in Europe], 17 June 2025
European Commission decision 28 March 2025
Information on Translarna, European Medicines Agency, 16 April 2025

Results regarding walking ability inconclusive after 10 years
• **Phase IIb trial** (2014): 174 patients (over five years old) treated with 40 or 80 mg/kg/day of Translarna® or a placebo. Mild deterioration in walking ability after one year in the group treated with 40 mg/kg/day compared to the placebo. The higher dose had no effect.
• **Phase III trial** (2017): 228 patients (seven to 16 years old) treated with 40 mg/kg/day. Only the patients who were able to walk well at the start of the trial deteriorated less (+47 m). The results were inconclusive for those who had lost their ability to walk. The effect was insignificant in all of the patients.
• **Phase III confirmatory trial** (2023): 300 patients (over five years old) treated with 40 mg/kg/day. Six-minute walk test scores did not differ significantly between the patients who were treated with Translarna® for 18 months and those who received the placebo.
• **STRIDE Registry** (2023): real-life data from over 300 patients treated with Translarna® for five and a half years on average between 2015 and 2022 compared to data from the CINRG registry concerning patients who were not treated with Translarna® (2006 to 2016). Although the patients in the STRIDE Registry lost their ability to walk three and a half years later than those in the CINRG registry, it was not possible to confirm that this was due to Translarna® as the data from this registry was unreliable.

Cell therapy - healing cells

Cell therapy involves either producing stem cells from a healthy donor in a laboratory, or taking cells from a patient and then modifying them by adding a specific function before putting them back into the patient. Transplanting stem cells in DMD patients is carried out with the aim of promoting the regeneration of target tissue (skeletal muscle, the heart) in order to make it functional.

__Stem cells__ possess both the ability to multiply to produce identical new stem cells (self-renewal) and the ability to give rise, under specific conditions, to differentiated cells (blood cells, liver cells, muscle cells, etc.).

CAP-1002 (deramiocel) - MAA submitted in the USA

This cell therapy, developed by the pharmaceutical company Capricor Therapeutics, aims to promote the cellular regeneration of cardiac muscle by using cardiac stem cells from healthy donors.

The open-label HOPE-2-OLE trial (NCT04428476) and the double-blind then open-label HOPE-3 trial (NCT05126758) are still taking place in the United States in more than 100 ambulatory or non-ambulatory participants over the age of 10 years old. CAP-1002 is administered via intravenous infusion every three months so that it reaches muscle tissue.

Phase II
Dose/effect

Phase III
Efficacy

A confirmed benefit

The pharmaceutical company Capricor Therapeutics confirmed that patients treated with CAP-1002 continued to show improvements in PUL scores after three years of treatment compared to data from untreated external controls. Stabilisation in left ventricular ejection fraction was also observed in patients treated with CAP-1002, indicating preserved heart function. In January 2025, an MAA was submitted to the FDA (the American regulatory authority) by Capricor Therapeutics.

Capricor Therapeutics press release 4 June 2024 and 2 January 2025
Capricor Therapeutics, Corporate Presentation, March 2025

The __Performance of Upper Limb scale (PUL)__ measures motor performance of the upper limbs and changes over time, even when the patient has lost their ability to walk. It takes into account muscle strength, growth and the presence of contractures. It was originally created for people with dystrophinopathies.
https://www.institut-myologie.org/imotion/the-tools/?lang=en

DT-DEC01 (chimeric cells) - one trial still taking place

The American pharmaceutical company Dystrogen Therapeutics developed a cell therapy product called DT-DEC01 which is made up of dystrophin-expressing chimeric cells that are partly derived from the patients who will receive the treatment. It is administered via intraosseous injection.

These chimeric cells are created by fusing two myoblasts (muscle precursor cells) - one from a healthy donor that expresses dystrophin and the other from the DMD patient receiving the treatment. Therefore, they express dystrophin and are able to target all *DMD* gene mutations, all while being tolerated by the recipient.

A phase I/II trial is still underway (EudraCT: 2022-003126-42) whose positive preliminary results were published in 2023.

Siemionow M. et al. Stem Cell Rev Rep 2023

Phase I
Safety/tolerability

Phase II
Dose/effect

Preclinical studies - transplanting modified cells using hydrogel

Stems cells from DMD patients were corrected using genome editing (CRISPR) and transformed into myogenic progenitor cells which are capable of repairing muscle. Stabilised in a special gel (hydrogel) and injected in mdx nude mice, they were able to be revascularised and reconnected to neuromuscular junctions for a long time, although with variable results depending on the different segments of the muscle fibres.

Kowala A. et al. Cell Rep Med. 2025

Protecting muscle from the effects of DMD and BMD

Other therapeutic approaches in DMD and BMD consist of minimising the harmful effects of *DMD* gene mutations on muscle health and health in general.

- **Managing the manifestations** that contribute to the vicious cycle of disease worsening (inflammation, fibrosis, oxidative stress, cardiac and respiratory involvement, gastrointestinal disorders).
- **Stimulating the production of molecules or proteins** which will functionally replace dystrophin (such as utrophin) or reduce the levels of others (such as myostatin) in order to increase muscle mass and improve strength.

Limiting inflammation - a wider range of drugs

In DMD, chronic muscle inflammation worsens the disease. This is linked to the process of repairing the damage that muscle cells weakened by a lack of dystrophin continuously undergo.

Corticosteroids - a safe bet

Oral corticosteroid therapy is the standard of care in DMD. It is prescribed from the age of four or five by a neuromuscular disease specialist. Corticosteroids delay loss of ambulation by three years on average, protect heart and lung function and continue to do so after loss of ambulation, and help preserve upper limb function and the ability to perform daily tasks (eating, transferring, turning over in bed, etc.).

__Synthetic corticosteroids__ (like prednisone and deflazacort) are drugs that mimic the action of __natural corticosteroids,__ which are hormones (like cortisol and cortisone) secreted by the adrenal glands (small glands situated above each kidney). These hormones control inflammation, the body's defence against attacks (immunity), the use of sugars and even stress management.

French guidelines for corticosteroid therapy

Created at the end of 2024 by FILNEMUS (a French healthcare network for rare neuromuscular diseases) and the Société Française de Neurologie Pédiatrique [French Society of Paediatric Neurology], these guidelines for corticosteroid therapy in children with DMD are based on international guidelines.

Two drugs covered. Prednisone/prednisolone (0.75 mg/kg/day) is sold in pharmacies and deflazacort (0.9 mg/kg/day) is available via compassionate access granted by the ANSM at the request of a patient's doctor. Vamorolone is not mentioned in these guidelines.

- **Treatment initiation.** Corticosteroid therapy should be started before significant physical decline (usually between the ages of four and six years old) following a comprehensive assessment (clinical examinations, laboratory tests, eye test, bone density scan, updating vaccinations, etc.).
- **Precautions for use**. The patient's family should be provided with information on food and the possible side effects of corticosteroid therapy, and instructions on how to take the medication correctly (preferably in the morning with breakfast, not to stop them abruptly, and not to give their child NSAIDs such as ibuprofen or aspirin while they are on corticosteroids).
- **Monitoring.** Tests conducted throughout follow-up allow the efficacy of the treatment to be assessed. Regular clinical examinations, eye tests, imaging and laboratory tests ensure that it is well tolerated.
- **Side effects.** Recommendations and advice for the management of the possible side effects (osteoporosis, weight gain, delayed puberty, cataracts (after four to six years of treatment), hypertension (22 to 47%

In France, in exceptional circumstances, the __compassionate access authorisation__ scheme ("accès compassionnel") enables a drug to be used without marketing authorisation, or in an indication other than that for which it has already been approved, to treat a severe or rare disease when there are no appropriate treatments available, when the patient cannot be included in a clinical trial or when treatment cannot be postponed. This scheme replaces the previous nominative "ATU" (autorisation temporaire d'utilisation) pathway. The drug in question is covered by Assurance Maladie (French health insurance system).

www.has-sante.fr/ [page in French]

of cases), behavioural problems, failure to thrive) are provided. Height should be measured every six months and any delay should prompt a consultation with a specialist. Growth hormone therapy and testosterone replacement therapy may be considered if puberty has not started by the age of 14.
Fontaine Carbonnel S. et al. Arch Pediatr. 2024

Do their effects on height and weight affect loss of ambulation?
In order to find out, data from 648 children with DMD from the UK NorthStar database treated with deflazacort or prednisone was analysed. The study confirmed that corticosteroids prolong walking ability (average age at loss of ambulation 15.8 years old with daily deflazacort and 14.9 years old with daily prednisolone). There was no link between the effects of corticosteroid therapy (slower growth, weight gain) and loss of ambulation. However, excessive annual weight gain beyond a certain threshold over a two-year period may increase the risk of loss of ambulation, while slower growth appears to decrease it.
Stimpson G. et al. Eur J Neurol. 2024

Vamorolone (Agamree®) - authorised but not available

Vamorolone is a "dissociative" corticosteroid developed by ReveraGen Biopharma and Santhera Pharmaceuticals. It was granted **marketing authorisation** in Europe in 2023.
However, even though it has marketing authorisation, it cannot be prescribed in France as marketing negotiations between the pharmaceutical company Santhera and the public authorities have not yet been concluded and the HAS (Haute Autorité de Santé [French National Authority for Health]) rejected a request for early access (an exceptional access scheme).

Milestones achieved for vamorolone (Agamree®)
• MA in Europe for the treatment of DMD from the age of four (December 2023).
• Oral route of administration (oral suspension).
• Even though the HAS is in favour of making vamorolone eligible for reimbursement from health insurers for DMD patients over the age of four, it nevertheless believes that it has no additional clinical benefits when compared to other corticosteroids (efficacy, safety and tolerability).
• The HAS refused to grant Agamree early access authorisation in France.
HAS, Agamree (vamorolone) - historique des avis [opinion timeline], 18 June 2024
AFM-Téléthon's contribution to the evaluation of vamorolone, 2023 [document in French]
Agamree (vamorolone), EMA

Early access programmes *enable access to innovative drugs whose safety and efficacy are strongly presumed in a given indication, which must be a severe, rare or debilitating disease for which no appropriate treatment is available. The word "early" indicates that the drug has not yet obtained marketing authorisation (MA) or been made eligible for reimbursement from health insurers for this indication. The pharmaceutical company will then undertake to request this from the health authorities.*
www.has-sante.fr/ [page in French]

A meta-analysis of the efficacy, safety and tolerability of vamorolone
Data from 210 DMD patients treated with vamorolone (2 mg/kg/day or 6 mg/kg/day) showed that:
• its efficacy was able to be confirmed using timed tests (timed four-stair climb and timed rise from floor) and was even better with the higher dose;
• it seemed to have less of an impact on growth than other steroids but did increase the risk of weight gain and insulin resistance.
However, the lack of external controls and objective evidence to determine the long-term effects of vamorolone constitutes bias.
Ibrahim MS. et al. Neurol Sci. 2024

Vamorolone and prednisone both suppress the adrenal glands

One of the side effects of corticosteroid therapy is adrenal suppression. The adrenal glands produce natural corticosteroids in the body. A trial comparing vamorolone to prednisone showed that both corticosteroids induced the same level of adrenal suppression, which was dose dependent for vamorolone.

Ahmet A et al. Clin Endocrinol Metab. 2025

Phase IV
Pharmacovigilance

Ongoing trials continue to evaluate vamorolone

- A phase IV trial (GUARDIAN) in Europe monitoring 80 participants from previous studies (trial completion: September 2028) (NCT06713135);
- A long-term, observational registry study involving 250 patients over the age of two years old treated with vamorolone in the United States (study completion: November 2030) (NCT06564974).

Also in trials for Becker muscular dystrophy

A vamorolone trial is currently taking place in ambulatory adults with BMD in the United States.

Phase II
Dose/effect

Placebo-controlled trial of vamorolone in BMD

United States and Italy	39 (18 to 64 years old)	Not recruiting	June 2022 – June 2025 28 weeks of follow-up

NCT05166109

Vamorolone improved skeletal muscle strength and structure in a new mouse model of the disease.

Heier C. et al. MDA Conference, March 2025

*A **biological marker** (or **biomarker** for short) is a measurable characteristic that indicates a normal or pathological biological process. The identification of new biological markers for a disease is very important for monitoring the progression of the disease and the efficacy of new treatments. These markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

Canakinumab (Ilaris®) - to be studied in the longer term

Canakinumab is a monoclonal antibody that neutralises interleukin-1 beta (IL-1β), a cytokine that increases in DMD during episodes of inflammation. It is used in children with inflammatory diseases such as juvenile idiopathic arthritis.

Preliminary results in DMD published this year

Phase I
Safety/tolerability

Phase II
Dose/effect

An American phase I/II trial of canakinumab (Ilaris®) (NCT03936894) evaluated biomarkers of inflammation in the blood of three boys with DMD who were naive to treatment with corticosteroids (two aged four and one aged five) four months after receiving a single subcutaneous injection of canakinumab at a dose of 2 mg/kg. A decrease was observed in proinflammatory markers and myostatin levels, but not in IL-1β levels. A longer treatment period is needed to demonstrate increased benefit. The product was well tolerated and did not cause any local reactions at the injection site.

Spurney CF. et al. Neuromuscul Dis. 2025

TAS-205 - a prostaglandin D2 synthase inhibitor

Developed by the Japanese pharmaceutical company Taiho Pharmaceutical, TAS-205 is being evaluated in DMD due to its effect on inflammation and muscle necrosis. It inhibits an enzyme which enables the production of prostaglandin D2. Prostaglandin D2 is found in the necrotic muscle of people with DMD.
A phase III trial is currently evaluating it after positive effects on walking ability were observed in boys over the age of five who received TAS-205 over 24 weeks.

TAS-205 trial (REACH-DMD)

Phase III
Efficacy

Japan	104 (over 5 years old)	Not recruiting	Nov 2020 – May 2027 1 year of follow-up

NCT04587908

ATL1102 (avicursen) - development discontinued

Developed by the pharmaceutical company Percheron Therapeutics, ATL1102 is an antisense oligonucleotide which targets mRNA that codes for CD49d (a subunit of VLA-4) in order to inhibit it and therefore reduce inflammation.

- A phase IIb trial (NCT05938023) conducted in 48 non-ambulatory boys aged 10 to 17 years old which was evaluating ATL1102 compared to a placebo did not meet its primary endpoint (changes in PUL 2.0 scores after six months of treatment) despite the product being well tolerated.

Percheron Therapeutics announced that it was discontinuing the programme.
Percheron Therapeutics press release 18 December 2024

*The **Performance of Upper Limb scale 2.0 (PUL 2.0)** measures motor performance of the upper limbs.*

Preclinical studies - KER-065 - blocking the activity of myostatin and activin A

The pharmaceutical company Keros Therapeutics designed KER-065 to trap molecules (ligands) that bind to activin type II receptors (ActRII). ActRII are involved in the activation of myostatin (a mediator of muscle loss) and activin A (a mediator of inflammation), therefore their effects are inhibited.
A study comparing the effects of KER-065 with those of prednisolone in an mdx mouse model showed that KER-065 provided better anti-inflammatory benefits than prednisolone, and that it increased muscle mass and improved grip strength in the mice treated.
KER-065 is currently being evaluated in healthy volunteers in a phase I trial.
Zhen G. et al. MDA Conference, March 2025

Phase I
Safety/tolerability

Inhibiting HDAC to boost muscle regeneration

Givinostat (Duvyzat™) - authorised in Europe for DMD

Givinostat inhibits HDAC, intracellular molecules that activate or inhibit certain genes.
Some HDAC are involved in the maintenance of healthy muscle (protection, regeneration, etc.), but in muscles affected by DMD or BMD they tend to go a bit crazy, activating inflammation, fibrosis and the production of myostatin via follistatin. Blocking them could therefore improve muscle structure and composition in these diseases.

Milestones achieved for givinostat (Duvyzat™)
- **Conditional marketing authorisation** granted by the European Commission (based on the positive assessment from the EMA) for ambulatory boys on corticosteroids **from the age of six** (oral suspension to be taken twice a day).
- **Access to givinostat is now possible in France** via the **compassionate access authorisation** scheme (authorised by the ANSM). FILNEMUS highlighted this scheme to neuromuscular specialists.

European Commission press release 6 June 2025
Duvyzat, Overview, European Medicines Agency, 25 April 2025

*In France, in exceptional circumstances, the **compassionate access authorisation** scheme ("accès compassionnel") enables a drug to be used without marketing authorisation, or in an indication other than that for which it has already been approved, to treat a severe or rare disease when there are no appropriate treatments available, when the patient cannot be included in a clinical trial or when treatment cannot be postponed.*
This scheme replaces the previous nominative "ATU" (autorisation temporaire d'utilisation) pathway. The drug in question is covered by Assurance Maladie (French health insurance system).
www.has-sante.fr/ [page in French]

Phase III
Efficacy

Efficacy results that still need to be backed up

As part of the phase III EPIDYS trial, 81 ambulatory DMD patients aged six to 17 years old were treated with givinostat for 18 months. They were compared to 39 patients who received a placebo. A significant improvement (-1.78 seconds) in four-stair climb test results was observed in the treatment group (the primary endpoint of the trial). However, the difference in strength and motor function between the two groups was not significant. An extension study is currently evaluating the long-term safety and efficacy of givinostat.
Mercuri E. et al. Lancet Neurol. 2024

What is "conditional" marketing authorisation?
The EMA may grant conditional marketing authorisation if all of the following criteria are met: the benefit/risk ratio of the medicine in question is positive, it is likely that the pharmaceutical company will be able to provide further data, the medicine fulfils an unmet medical need and the benefit of the medicine's immediate availability to patients outweighs the risk inherent in the fact that additional data is still required.
Conditional marketing authorisation are valid for one year and can be renewed annually. The pharmaceutical company must commit to collecting additional data.
https://www.ema.europa.eu/en/homepage

- **Two trials are currently taking place in France:** the open-label extension of the EPIDYS trial (NCT03373968) and the ULYSSES trial.

Phase III
Efficacy

Givinostat trial (ULYSSES) in non-ambulatory DMD patients

France and abroad	138 (9 to 17 years old)	Recruiting	Feb 2024 - Feb 2028 1.5 years of follow-up

NCT05933057

More information on givinostat trials in France [page in French]

Targeting the myosin in fast-twitch muscle fibres

EDG-5506 (sevasemten) - promising in BMD

EDG-5506 is a small molecule developed by the pharmaceutical company Edgewise Therapeutics. **It modulates the recruitment of the myosin in fast-twitch muscle fibres.** Fast-twitch muscle fibres are particularly used during repeated contractions in dystrophies and become damaged. EDG-5506 preserves muscle integrity by limiting their recruitment. It has been granted orphan drug designation for DMD and BMD.

Myofibrils *are contractile structures within muscle fibres. They are comprised of myosin and actin, filaments that slide over each other during muscle contraction.* ***Slow-twitch muscle fibres*** *are recruited for endurance activities that are gentler on the muscles.* ***Fast-twitch muscle fibres*** *are recruited for powerful and fast movements during intense physical activity.*

EDG-5506 (sevasemten) is a drug candidate that comes in tablet form to be taken once a day.

New results from BMD trials

▪ **The ARCH trial** (NCT05160415). After two years of treatment, meaningful levels of motor function in 12 ambulatory patients aged 18 to 55 years old were significantly preserved by EDG-5506 compared to expected rates of decline from BMD natural history data.
Niks EH. et al. MDA Conference, March 2025

▪ **The CANYON trial** (NCT05291091). In this first part of the GRAND CANYON programme, EDG-5506 was well tolerated in 40 adults (18 to 50 years old) and 29 adolescents (12 to 18 years old). Results from the adults after 12 months of treatment compared to a placebo showed:
. a 28% decrease in CK levels in the blood;
. relatively stable NSAA scores throughout treatment (63% of the patients treated with EDG-5506 had stable or improved scores) and, after 12 months, a positive 1.12 point-difference between the treatment group and the placebo group. Four-stair climb results were better (0.22 seconds vs 0.34 seconds), as were those for the 10-metre walk/run test.
Mc Donald MG. et al. MDA Conference, March 2025
Craig McD. et al. MDA Conference, March 2025

The North Star Ambulatory Assessment (NSAA) *scale measures a patient's ability to perform various tasks (walking, running, jumping, climbing stairs, getting up from the floor, etc.). This scale provides a fairly accurate interpretation of the experiences of patients in daily life.*

EDG-5506 was well tolerated and biomarkers decreased in the first phase I trial conducted in healthy volunteers and adults with BMD.
Donovan J. et al. Muscle Nerve. 2025

A trial still underway in BMD

GRAND CANYON trial (placebo-controlled)

France and abroad	175 (18 to 50 years old)	Not recruiting	July 2022 – Aug 2026 1.5 years of follow-up

NCT05291091

Phase II
Dose/effect

More information on the GRAND CANYON trial in France [page in French]

EDG-5506 in DMD

▪ The phase II LYNX trial (placebo-controlled and double-blind, then open-label) is evaluating EDG-5506 in 76 ambulatory participants with DMD aged between four and nine years old in the United States (expected to end in 2026) (NCT05540860).
▪ The phase II FOX trial is evaluating EDG-5506 administered for one year in 43 participants with DMD aged six to 17 years old who were previously

treated with AAV gene therapy for at least two years in the United States (expected to end in October 2025) (NCT06100887).

Reducing fibrosis and increasing muscle mass

The replacement of muscle tissue by inelastic, fibrous scar tissue occurs during muscle degeneration (loss of muscle cells). Limiting this irreversible event (which is specific to muscles affected by dystrophy) should help preserve muscles and their strength. That said, drugs evaluated so far have not been effective.

Tamoxifen - no benefit for non-ambulatory patients either

Published in February 2025, the results of the second part of the phase III TAM-DMD trial which involved non-ambulatory DMD patients aged 10 to 16 years old off corticosteroid treatment for at least six months showed that there were no significant differences in motor function between the group treated with 20 mg of tamoxifen a day for one year (eight participants) and the placebo group (six participants). Inconclusive results were also published for ambulatory patients (October 2023).
Even though it is well tolerated, tamoxifen is not recommended in DMD.
Henzi BC. Et al. Neuromuscul Disord. 2025

Registries and databases

Healthcare databases, registries and data warehouses, and observational studies are used to define the natural history of a disease, monitor its prevalence, improve its diagnosis and treatment, and facilitate the implementation of clinical trials.

The registre français des dystrophinopathies

Created in 2019, the registre français des dystrophinopathies (or registre DYS), supported by AFM-Téléthon, collects health data (medical and genetic) from children and adults (male and female) with a dystrophin gene mutation (including those who have DMD or BMD) who are being monitored at FILNEMUS neuromuscular disease centres.
This data is collected in the registry from information entered in medical records before or after 2019. Used in 35 specialist neuromuscular disease centres, the registre DYS has 1,394 patients registered as of 14 May 2025.
The registre français des dystrophinopathies | AFM Téléthon (afm-telethon.fr) [page in French]

*The **TREAT-NMD Alliance** is an international network for neuromuscular diseases which brings together scientists, clinicians and patient groups. Originally supported by the European Commission as an EU Network of Excellence, the TREAT-NMD Alliance facilitates conditions which ensure that the most promising research reaches patients. It also seeks international recognition of the best current care practices for people with neuromuscular diseases.*
TREAT-NMD

Other registries around the world
1. The Duchenne Registry created by Parent Project Muscular Dystrophy (NCT02069756) www.duchenneregistry.org/ (United States).
2. Treat-NMD also runs DMD and BMD registries in Europe.
Duchenne/Becker muscular dystrophy - TREAT-NMD

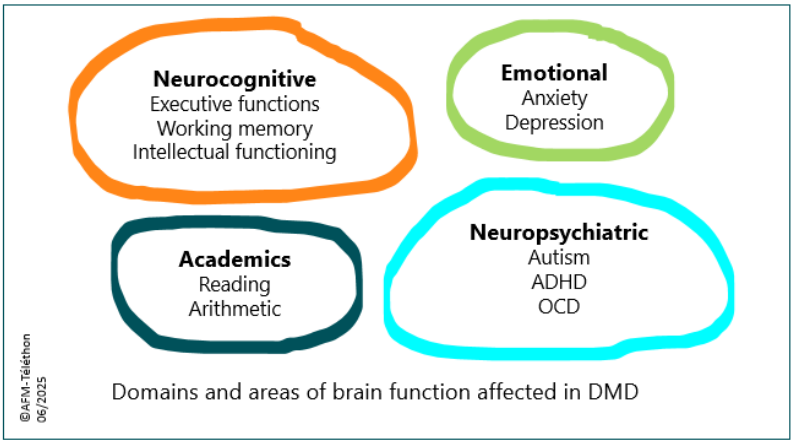
Daily management and treatment

The brain taking centre stage

Results of the BIND studies currently being analysed

In 2024, the data collection part of the European BIND (Brain INvolvement in Dystrophinopathies) project took place which involved clinicians, researchers, patient organisations and seven neuromuscular centres in Europe, including one in France (Hôpital Necker- Enfants Malades). With its two studies (BIND 1 - NCT04583917 - and BIND 2 - NCT04668716), its objective was:
- to characterise cognitive impairment in DMD and BMD patients (questionnaires, interviews, neuropsychological assessments),
- to understand the role of dystrophin isoforms in the brain and its links with cognitive impairment (MRI scans);
- to reach a consensus on the best tools for the clinical assessment and diagnosis of neurocognitive and neurobehavioural disorders, and for research.

▪ An article published in 2024 provided a profile of the BIND study respondents (323 children with DMD and 36 with BMD aged five to 17 years old, and 74 adults with BMD aged 18 to 50 years old) and a trend analysis:
- the outcome measures used in the studies were sensitive and appropriate and were therefore able to be used in clinical cognitive assessments;
- they helped better identify the profile of cognitive difficulties in patients in four domains (which can overlap, complicating screening and evaluation).



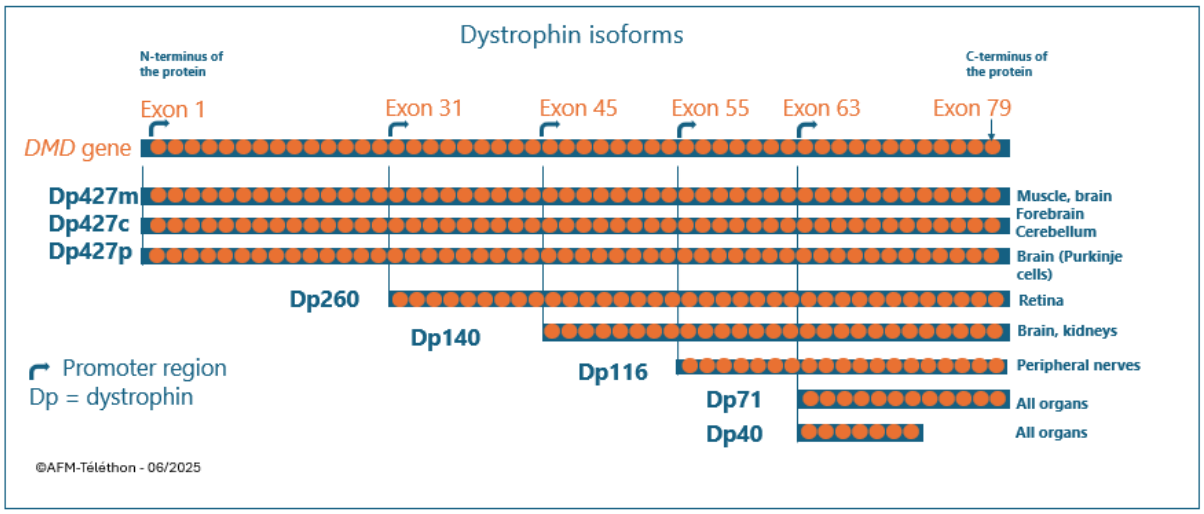
Domains and areas of brain function affected in DMD

- behavioural and psychosocial problems are underestimated (even when they are diagnosed) and are not adequately treated by available drugs;
- there are correlations between the dystrophin isoforms present in certain regions of the brain and the type of cognitive impairment.
Hendriksen J et al. Neuromuscul Disord. 2024

Dystrophin isoforms and cognitive impairment

The *DMD* gene (79 exons) produces eight types (isoforms) of dystrophin of varying lengths. Almost all of them contain the end of the gene (except Dp40), but not the beginning. They are found in different organs, with the longest (Dp427) being produced in muscle. The shortest (after Dp40) is Dp7 which is present in all organs including the brain.

DMD gene mutations prevent the production of certain isoforms (depending on their location in the gene) which has different effects on function and cognition.



▪ An article summarised data showing the link between cognitive impairment in DMD and the absence of certain dystrophin isoforms. Intellectual disability, autism, attention deficit hyperactivity disorder (ADHD), anxiety and obsessive-compulsive disorder (OCD) were linked more to the absence of the Dp427 isoform, and worsened by the absence of Dp140. The absence of Dp71 and Dp140 was associated more with impaired intellectual functioning (executive functions, working memory, intellectual disability, etc.) and behavioural disorders. In animal models of DMD (mice, etc.), the research team was also able to show that the absence of Dp427 led to increased stress reactivity, and the absence of Dp140 worsened social behaviour problems.
The article reviewed possible pharmacological treatments, including methylphenidate (Ritalin®) for ADHD, risperidone (an antipsychotic) for ASD and fluoxetine (Prozac®) for anxiety disorders, stating that there is still a lack of guidelines for their use in patients with additional cardiorespiratory comorbidities. Cognitive behavioural therapy (CBT) and problem-solving therapy were also mentioned. The positive results of gene therapies administered in DMD mice which restore brain dystrophins suggest that both brain and muscle dysfunction could be treated.
Vaillend C et al. Nat Commun. 2025

***Cognitive functions** are functions coordinated by the brain. These include language, know-how, visual recognition and executive functions, i.e. functions that organise and control voluntary actions. During every action or activity (intellectual or manual), different cognitive functions, and therefore different parts of the brain, are called upon.*
Like other bodily functions, they can be disrupted.
Les troubles cognitifs, parlons-en [Let's talk about cognitive impairment].

Impaired social cognition in DMD?
The cognitive abilities (memory, attention, etc.), including social cognition, of 20 Italian boys with DMD aged seven to 17 years old were evaluated and their scores compared to the standard values established for these tests. Scores reflecting their ability to understand the intentions of others and recognise facial expressions (emotions, moods, etc.) were poorer when compared to the standard values. These differences were observed regardless of whether the boys had another cognitive deficit.
Only two previous studies have reported impaired social cognition in dystrophinopathies. Even though it was only deducted from a small number of patients, this additional data supports the possibility of social cognition impairment being one of the neurological manifestations of

DMD. This highlights the need for impaired social cognition to be evaluated in a larger-scale study.
Parravicini S. et al. Front Psychol. 2025

Cognitive impairment in women with *DMD* gene mutations

A study was conducted in 33 women with *DMD* gene mutations and an average age of 38. Of these 33 women, 48.5% had abnormal cognition, with multiple domains affected (attention in 51.5%, verbal fluency in 36.4%, memory in 21.2% language in 27.3% and visuospatial ability in 36.4%). Only 15% had symptoms of depression. MRI scans performed on these patients were compared to those of 33 healthy women. They highlighted changes in the structure of the parieto-occipital cortex (an area of the cerebral cortex located at the back of the brain) which is particularly involved in visual perception, as well as abnormalities that correlated with the attention, memory and verbal fluency scores.
When present, these problems should encourage women to talk to their doctor, so that a neuropsychological assessment and cognitive remediation therapy can be offered to them.
de Brito MR. et al. J Neurol. 2025

A rewatchable webinar
Organised by FILNEMUS, the "Cognition dans les maladies neuromusculaires : exemple de la dystrophinopathie et de l'amyotrophie spinale [Cognition in neuromuscular diseases: dystrophinopathy and spinal muscular atrophy]" webinar was presented by Professor Isabelle Desguerre, paediatric neurologist (Hôpital Necker-Enfants Malades, Assistance Publique – Hôpitaux de Paris [Greater Paris University Hospitals]).
It is available to rewatch on the FILNEMUS website.
FILNEMUS, I. Desguerre, FILNEMUS webinar, 20 March 2025 [webinar in French]

Natural history of BMD better documented

Retrospective data from 943 Italian BMD patients indicated a very variable age of diagnosis (ranged from four to 14 years old), with diagnosis prompted by elevated CK levels in more than half of the cases. Less often, the onset of the disease manifested itself through muscle pain or cramps, walking difficulties, delayed motor development and falls.
The majority (86%) of *DMD* gene mutations found were in-frame deletions (exon deletions that do not shift the reading frame of the gene). Some of them (such as exon 45-49 deletions) predisposed to losing the ability to run and walk a little earlier, around the ages of 25 and 41 respectively, while others (exon 45-48 deletions) preserved them for longer (up to 30 and 66 years of age). Exon 45-55 and exon 48 deletions were more associated with a decreased likelihood of developing left ventricular dysfunction than exon 45-47 deletions. Finally, the authors of the study highlighted the presence of modifier genes which also influence the prognosis of the disease.
Gorgoglione D. et al. Brain. 2025

*Every gene is organised into an alternating arrangement of coding sequences (**exons**) and non-coding sequences (**introns**).*
The term "coding" is used to refer to the portions of genes that are used by cellular machinery as a blueprint for making proteins, therefore only exons are translated into proteins.

The heart - a vital muscle to protect

Predictors of heart disease in DMD

A literature review (in which French clinicians participated) that included 33 articles encompassing 9,232 patients highlighted predictors of heart disease in DMD:

***Cardiomyopathy** is a disease of the heart muscle. It can be asymptomatic (no visible symptoms) or cause significant fatigue, breathing difficulties, arrhythmia or chest pain (less common).*

• taking heart medication (ACE inhibitors, beta blockers, etc.) was significantly associated with preserved heart muscle function (high-quality evidence);
• taking deflazacort (corticosteroid) was also associated with preserved heart muscle function; corticosteroid therapy in general was also linked to a lower risk of cardiomyopathy and heart failure-related mortality;
• full-time mechanical ventilation seemed to be correlated with a lower risk of cardiomyopathy (low-quality evidence).
• the presence of certain *DMD* gene mutations was significantly correlated with a mild risk of cardiomyopathy (mutations in exons 51 and 52 in the *DMD* gene, deletions treatable by exon 53 skipping (see page 18) and mutations around exon 55).
In contrast, mutations in exons 45 to 50 seemed to be associated with earlier heart disease (low to very low-quality evidence).
Landfeldt E. et al. Orphanet J Rare Dis. 2024

▪ **Angiotensin-converting-enzyme (ACE) inhibitors** limit the synthesis of angiotensin which lowers blood pressure and protects the heart. **ACE inhibitors** are prescribed from the age of 10 as a preventative treatment in DMD and as early as possible in BMD depending on the course of the disease.
▪ **Beta blockers** are used to treat established heart failure.
Treatment with beta blockers can be offered in DMD. These drugs protect the heart by slowing the heart rate down and reducing the force at which cardiac muscle contracts.

Heart transplant - resistances lift little by little

Over the last 30 years, 275 cases of heart transplants being carried out in people with muscular dystrophy have been published, with more and more reported every year. There is now less reluctance to operate on people with a muscle disease, especially since heart transplants tend to improve muscle function and prolong life. However, it's still a decision that needs to be a made on a case by case basis. The indication for heart surgery should be clearly defined and anti-rejection medication suitably adjusted.
The rate of operative and postoperative complications in people with muscular dystrophy is no higher than that of other heart transplant patients. Pre- and postoperative rehabilitation should be intensified in order to limit the risk of respiratory infections/failure.
Politano L. et al. Int J Mol Sci. 2024

Guidelines for transitioning from paediatric to adult care in DMD

A group of 15 international experts established guidelines and 48 consensus recommendations for the transition of DMD patients from paediatric to adult care. These recommendations cover preparing for the transition (informing young people and their families of the process and plan from the age of 15 and regularly discussing it with them, appointing a coordinating healthcare professional to organise the process and coordinate the transition plan with caregivers, the young person and their family), transferring medical records from the paediatric centre to the adult centre, maintaining a point of contact at the adult centre, and the need for the transition to take place no later than the age of 25.
Castro D. et al. Eur J Paediatr Neurol. 2025

Urinary problems - should we be talking about them?

A lack of dystrophin also impairs smooth muscles such as those of the urinary tract (bladder, urethra, etc.), leading to frequent problems.

- In a Turkish study conducted in 45 boys with DMD aged five to 18 years old, nine out of 10 boys had lower urinary tract symptoms. Nearly two thirds used strategies to hold it in (crossing their legs or holding their crotch), half had an urgent need to urinate, and 46% and 31% experienced daytime and nighttime leaks respectively. These problems are not however always looked for by doctors.
- In Denmark, these problems were the subject of a survey conducted in 700 women with several different neuromuscular diseases, including dystrophinopathies. Thirty-nine percent of these women found going to the toilet when not at home problematic, and many of them reported wasting a lot of time and energy planning their toilet visits before leaving the house. They also reported avoiding going to the toilet outside their home, adopting various strategies such as not drinking, urinating less often and holding it in, sometimes for a very long time. The impact on their health should be taken seriously (17% experienced recurrent urinary tract infections). Very few of the respondents were referred to a urologist.

Öztürk D et al. Neurourol Urodyn. 2024
Werlauff U. et al. J Neuromuscul Dis. 2024

Common gastrointestinal disorders and complications

These disorders (usually dysphagia, gastro-oesophageal reflux disease, delayed gastric emptying, constipation and intestinal pseudo-obstruction) are often overlooked but have a significant impact on DMD patients in terms of quality of life and daily nutritional management.

They arise from problems in the motility of gastrointestinal smooth muscle caused by the absence of dystrophin and its effects on the gastrointestinal tract. Pathophysiological mechanisms that explain these problems have been identified. They include impaired calcium homeostasis, disrupted nitric oxide (NO) signalling, inflammation and fibrosis of gastrointestinal smooth muscle, and defective interstitial cells of Cajal (which generate contractions in gastrointestinal smooth muscle).New therapeutic approaches could benefit from understanding these mechanisms.

Subhan F. et al. Neurogastroenterol Motil. 2024

It's all go - international events

In France and internationally, conferences, congresses and workshops enable the scientific and medical community, patients and patient organisations to come together to improve research, treatments and the everyday lives of people with DMD.

Duchenne Care Conference

Organised by the World Duchenne Organization (WDO) and supported by EURO-NMD, the Duchenne Care Conference takes place every year in May and is open to all upon registration. Sessions are available to view on demand on the WDO website. The last conference took place on 26 and 27 May 2025 and some sessions are available for on-demand viewing.

www.worldduchenne.org/duchenne-care-conference/

***EURO-NMD** is a European Reference Network for the thematic grouping of rare neuromuscular diseases.*
https://ern-euro-nmd.eu/about/

World Duchenne Awareness Day (7 September)

Officially recognised by the United Nations, World Duchenne Awareness Day takes place on the seventh day of the ninth month, a symbolic date representing the 79 exons of the *DMD* gene.

- Every year, a new theme fuels discussions on the disease and creates connections around the world. In 2024, the theme was "Raise your voice for Duchenne".

The theme for 2025 is "Family: the heart of care".

www.worldduchenneday.org/2024-raise-your-voice-for-duchenne/
www.worldduchenneday.org/2025-family-the-heart-of-care/

- On 7 September 2024, in honour of World Duchenne Awareness Day, the AFM-Téléthon Groupe d'Intérêt Duchenne-Becker organised a day of discussions centred on dystrophinopathies for patients and their families via video conferencing. These discussions focused on different topics, from scientific advances to daily life and disease management. Newsletter no. six, published to coincide with this event, can be found on the group's blog [in French].

https://dmdb.afm-telethon.fr/newsletter-n6/

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Keep up to date on Duchenne muscular dystrophy and Becker muscular dystrophy research news throughout the year on the AFM-Téléthon website:
www.afm-telethon.fr/en/latest-news