JUNE 2022

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

ADVANCES in *SMN1*-related proximal spinal muscular atrophy

> *SMN1 gene-related proximal spinal muscular atrophy*
> Spinal muscular atrophy *(SMA)*
> *Spinal muscular atrophy 5q*
> *Infantile spinal muscular atrophy (ISMA)*
> *ISMA type I and II*
> *Werdnig-Hoffmann disease*
> *ISMA type III*
> *Kugelberg-Welander disease*
> *ISMA type IV*

SMN1-related proximal spinal muscular atrophy is a type of proximal spinal muscular atrophy, a rare group of genetic diseases causing degeneration of the nerve cells conveying, from the spinal cord to the muscles, messages ordering movement: the peripheral motor neurons. A decrease in the number of muscle fibres, which cannot survive without innervation, causes a lack of strength and muscle wasting (muscular atrophy). There are four types of *SMN1*-related proximal spinal muscular atrophy, according to age of onset and severity of the signs.

This document, published for the AFM-Téléthon 2022 General Assembly, presents research news from the past year regarding *SMN1*-related proximal spinal muscular atrophy: ongoing clinical trials or studies, clinical/scientific publications, international symposia, etc. It can be downloaded from the AFM-Téléthon website, where other information can also be found in the scientific, medical, psychological, social or technological fields relating to *SMN1*-related proximal spinal muscular atrophy:

WEB www.afm-telethon.fr/en

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

Table of Contents

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Three treatments available for SMA

Spinraza®

- An **antisense oligonucleotide** that acts on the maturation of the ***SMN2* gene**.
- Regular **intrathecal** administration

Zolgensma®

- A **gene therapy product** that delivers, using a viral vector, **the *SMN1* gene**
- Single **intravenous** administration

Evrysdi®

- A **small drug molecule** that acts on the maturation of the ***SMN2* gene**.
- Daily **oral** administration

An active field of research

563 scientific articles

published between May 2021 and May 2022

(Source: PubMed)

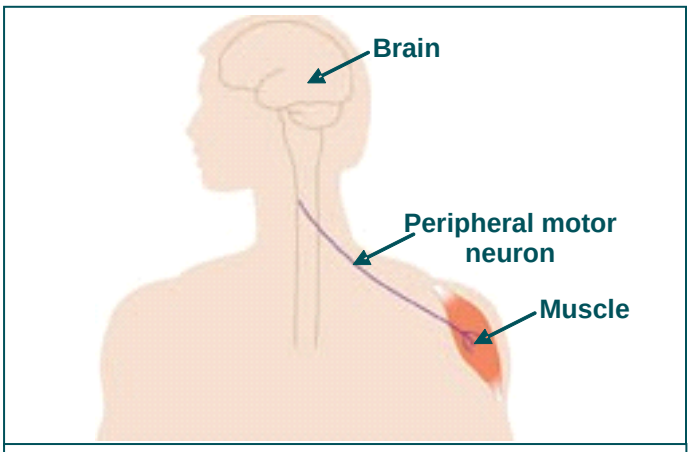
79 clinical trials

ongoing or in preparation worldwide as of 31 May 2022

(Source: ClinicalTrials.gov)

What causes *SMN1*-related proximal spinal muscular atrophy?

The spinal muscular atrophies are rare genetic neuromuscular diseases. They are caused by DNA abnormalities and affect the peripheral motor neurons.



Role of the peripheral motor neuron in movement
The brain commands: the order to move is issued by the brain. This order is transmitted to the peripheral motor neuron, which conveys it down to the neuromuscular junction, where the message is transmitted to the muscle, which contracts.

Of the different forms of genetic spinal muscular atrophy, the **proximal spinal muscular atrophies** have the special characteristic of initially affecting the muscles of the limbs that are closest to the trunk (proximal muscles), such as the muscles of the shoulders and hips.

▪ The most common form of proximal spinal muscular atrophy (SMA) is the ***SMN1* gene-related form**. There are several types of this form (types I to IV) according to age of onset of the disease and degree of muscle strength deficit.

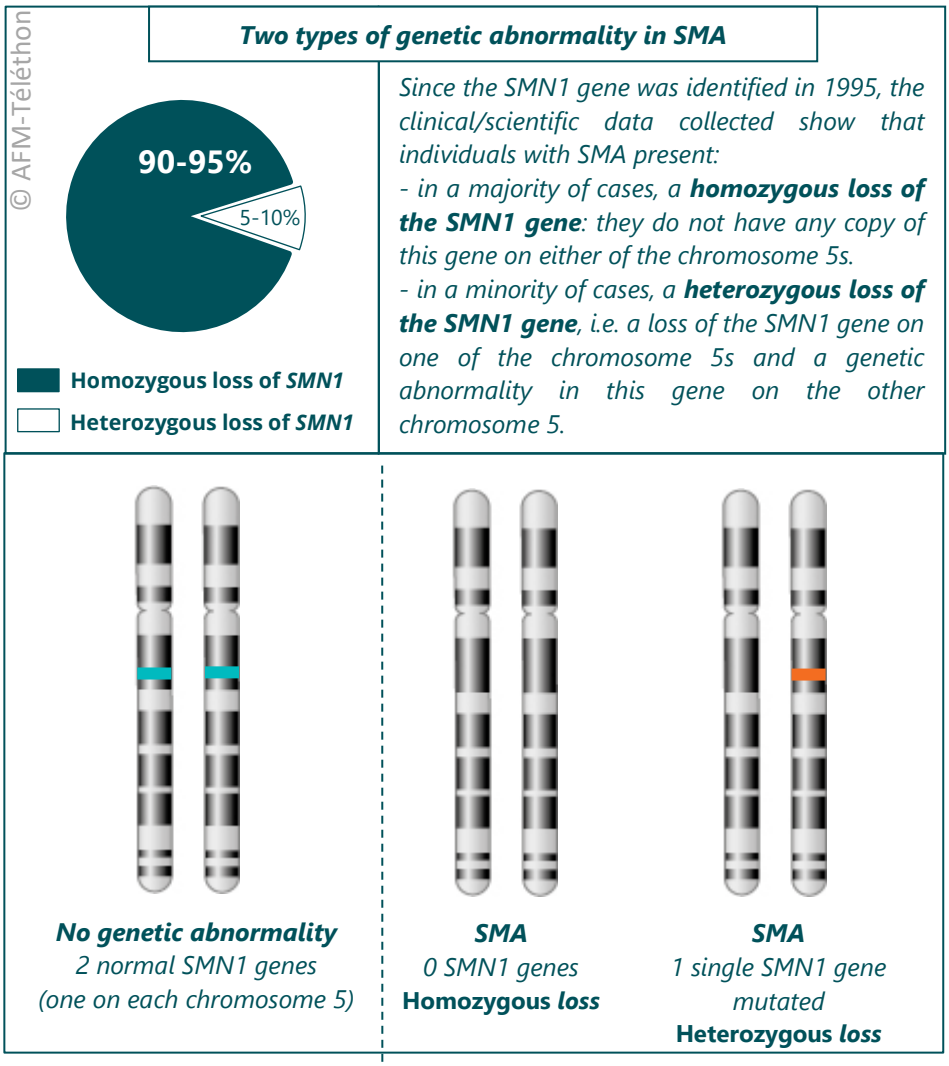
A defect in the *SMN1* gene is responsible

SMN1-related proximal spinal muscular atrophy (SMA) is caused by genetic abnormalities in the ***SMN1* gene**, located on chromosome 5. They are transmitted in an autosomal recessive manner.

Genetic diseases *are diseases caused by DNA abnormalities, i.e. abnormalities in the information that determines our body's biological functioning, present in our cells in the form of chromosomes. We inherit this information from our parents and our children inherit it from us. This is why genetic diseases are often familial (several members of the same family affected by the genetic disease).*
The genetic abnormalities can come in different forms: change in DNA code (mutation), loss of a piece of the gene (deletion), doubling of a piece of the gene (duplication), etc.

A ***motor neuron*** *is a neuron (nerve cell) that transmits/conveys motor orders (in the form of nerve impulses) from the brain and the spinal cord towards the muscles that perform the commanded movement. The central motor neurons, located in the brain, integrate and convey the nerve impulses from the cerebrum and cerebellum towards the spinal cord. The peripheral motor neurons receive the nerve impulses from the central motor neurons and convey them to the muscles.*

A hereditary disease is transmitted ***recessively*** *if both copies of the gene belonging to the person with the disease – the copy received from the father and that received from the mother – carry the genetic abnormality. The disease only manifests if both copies of the gene have the abnormality.*

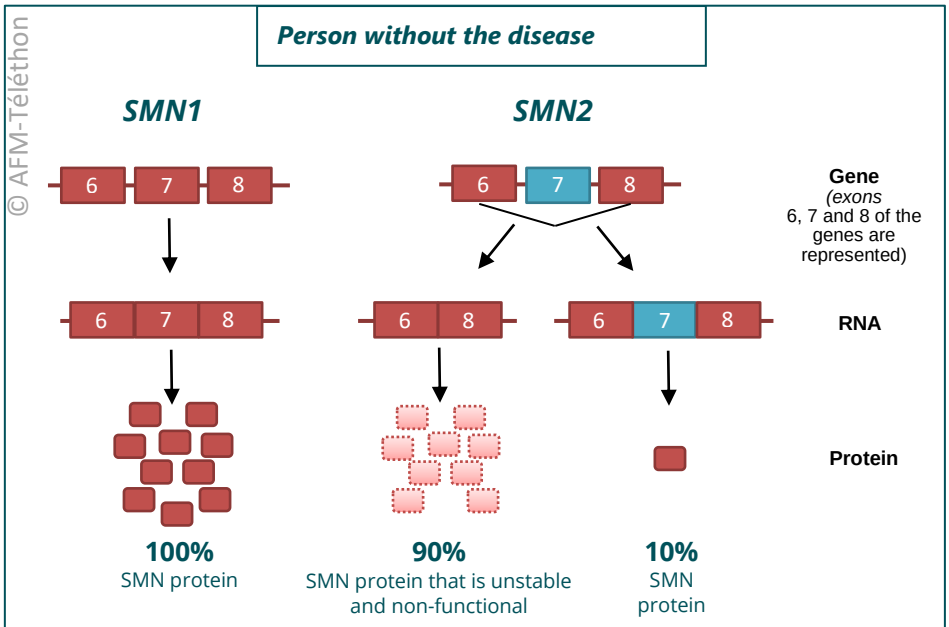


▪ A complete loss of the *SMN1* gene or abnormalities in this gene cause a degeneration of the peripheral motor neurons.
▪ The *SMN1* gene codes a crucial protein, the **Survival Motor Neuron (SMN) protein**. In SMA, *SMN1* gene abnormalities cause the production of this protein to be stopped.
▪ The **SMN protein** is found in all cells (it is said to be ubiquitous), but it is not yet known how an SMN protein deficit specifically results in peripheral motor neuron degeneration.

One or more *SMN2* gene copies

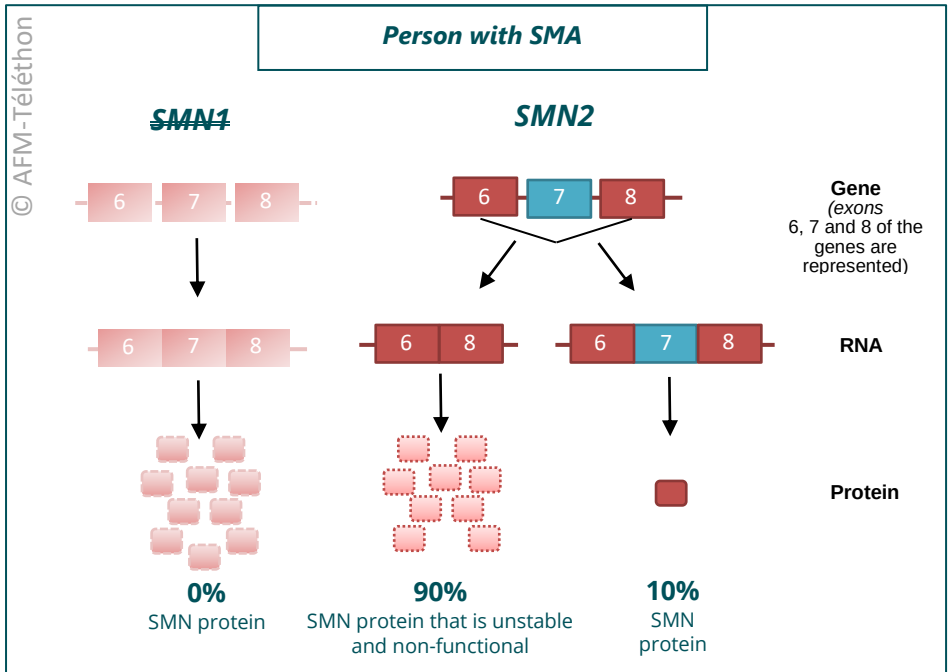
▪ In all individuals with SMA and in 95% of the general population, there is, next to the *SMN1* gene, an ***SMN2* gene**, the sequence of which is virtually identical. The difference is located at a nucleotide (a "letter" of the genetic message), found in a part of the gene called exon 7.
▪ This variation has major consequences on the production of the SMN protein: while the *SMN1* gene synthesises an SMN protein that is complete, functional, and does so in sufficient quantities, the *SMN2* gene mostly (90%) produces a shortened SMN protein that is fragile, barely functional, rapidly destroyed, and to a much smaller extent (10%), produces a normal SMN protein identical to that produced by the *SMN1* gene.

*Genes are structured as alternating coding sequences, the **exons**, and non-coding sequences, the introns. The exons are the parts of the gene that are used by the cell machinery as an assembly guide for protein production.*



The *SMN1* gene, the *SMN2* gene and the SMN protein in individuals without the disease

Normally, the SMN1 gene produces a sufficient quantity of SMN protein



The *SMN1* gene, the *SMN2* gene and the SMN protein in SMA

Individuals with SMA present a loss (homozygous or heterozygous) of the SMN1 gene. However, they have at least one copy of the SMN2 gene, which differs from SMN1 by one mutation in exon 7, causing:

- in 90% of cases, the production of an SMNΔ7 protein that is unstable and non-functional, lacking the part coded by exon 7;

- in 10% of cases, the production of an SMN protein that is complete and functional.

The percentage of both types of protein produced can vary depending on the tissues involved. The quantity of functional SMN protein produced using the SMN2 gene is, however, insufficient to compensate completely for the loss of the SMN1 gene.

Number of copies of the *SMN2* gene varies from individual to individual

The number of copies of the *SMN2* gene can vary from 1 to 6 in patients with *SMN1*-related proximal spinal muscular atrophy. In general, the more copies of the *SMN2* gene present, the less severe the disease. However, this general rule is not always true.

▪ A Spanish study that appeared in 2018, regarding more than 3000 patients with SMA of all types, helped to describe the number of copies of the *SMN2* gene present according to SMA type.

Number of copies of the *SMN2* gene	*Clinical phenotype*		
	SMA I	***SMA II***	***SMA III/IV***
1	7%	*<1%*	0%
2	73%	*16%*	5%
3	20%	*78%*	49%
4 and more	<1%	*5%*	46%

Calucho M et al. Neuromuscul Disord. 2018 March.

Clinical practice guidelines

A French national diagnosis and care protocol

French national diagnosis and care protocols (PNDSs)

The objective of the French PNDS documents (French National Diagnosis and Care Protocols) is to provide explicit guidelines to healthcare professionals regarding the optimal therapeutic management and the treatment pathway for patients with a specific rare disease. It helps to optimise and harmonise the therapeutic management and follow up of the rare disease in question, across the entire country.
Accompanied by scientific arguments and a summary intended for general practitioners, the full range of PNDSs can be consulted on the HAS (French National Authority for Health) website:
WEB www.has-sante.fr/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds

*The **FILNEMUS rare neuromuscular diseases healthcare network** hosts, coordinates and encourages interactions between stakeholders participating in the diagnosis, treatment and research of new muscular diseases (reference centres and centres of expertise, diagnostic laboratories, research teams, associations for individuals affected by these conditions, etc.). It was created in February 2014, as part of the second Rare Diseases French National Plan, 2011-2014.*
WEB www.filnemus.fr
➤➤ Organisation of care and neuromuscular diseases, Knowledge & Understanding reference documents, AFM-Téléthon

Created by the FILNEMUS rare neuromuscular diseases healthcare network, the Infantile Spinal Muscular Atrophy PNDS appeared in March 2021.

Besides providing **good clinical practice guidelines and highlighting the key medical issues**, the PNDS provides a list of useful addresses and websites (such as those of AFM-Téléthon or Orphanet), and the contact details for neuromuscular disease reference centres and centres of expertise.
HAS, March 2021

Tracheotomy Guidelines

Guidelines on tracheotomy in slowly progressive neuromuscular diseases were published by the HAS (French National Authority for Health) at the beginning of December 2022.

This work, conducted at the request of AFM-Téléthon, with the support of the SPLF (French-Language Society of Pneumology), the SRLF (French-Language Society of Intensive Care), the FILNEMUS rare neuromuscular diseases healthcare network and the ANTADIR (French National Association for Home Treatments, Innovations and Research), **specifies the indications**

and the conditions for performing a tracheotomy for patients with slowly progressive neuromuscular diseases requiring assisted ventilation.

The purpose of these guidelines is to improve the therapeutic management of these patients, the quality and safety of care provided to them, and their quality of life.

A tracheotomy should only be considered after failure of non-invasive ventilation (NIV) and cough assistance techniques. It must be performed with the written consent of the patient after they have received information and have been fully informed, and after a multidisciplinary team consultation meeting with neuromuscular disease specialists.
HAS, December 2020

2022, a third year marked by the COVID-19 pandemic

COVID-19 has continued to impact research in 2022. Certain clinical trials that should have started have been postponed. Several teams have, additionally, conducted specific studies on COVID-19 and its vaccination in cases of neuromuscular disease.

Researchers fully engaged

Experts in the FILNEMUS rare neuromuscular diseases healthcare network, with the support of AFM-Téléthon, have been conducting:
- since the beginning of the pandemic, a **national follow up** of COVID-19 cases among patients with neuromuscular diseases including facioscapulohumeral muscular dystrophy;
- surveys to measure the **impact of the pandemic** on this population;
- a study called CANNEMUSS on **the efficacy of vaccination** against COVID-19 in cases of significant muscle atrophy.

▪ Since March 2021, Bordeaux University Hospital has been conducting the Va-C-NEMUS national study in order to **learn more about the effects of COVID-19 and its vaccines** in neuromuscular patients.

Did you know?

Whether vaccinated or not, **any adult with neuromuscular disease** may participate in the Va-C-NEMUS observational study. After an initial questionnaire, each participant receives, once a month for a period of one year, a text message inviting them to answer a follow-up questionnaire online.

Va-C-NEMUS observational study

In France

5000 participants (18 years and over)

Ongoing recruitment

1 year of follow up (online)

March 2021

Va-C-NEMUS

Guidelines on vaccination

▪ All of this knowledge and the results of these studies have shown that vaccination is recommended in patients with neuromuscular disease, and more specifically, with SMA. It is especially important in cases of ventilatory insufficiency, with or without ventilation.
FILNEMUS guidelines on vaccination, December 2021

Less infection with COVID-19

▪ The results of a study conducted by FILNEMUS, with AFM-Téléthon, have shown that patients with neuromuscular diseases in France contracted COVID-19 in smaller numbers as a proportion of population compared to the general population during the first French lockdown (25 March 2020–11 May 2020): 17/10,000, versus 26/10,000 in the general population. Of the 84 people who developed COVID-19 symptoms and/or tested positive, none of them had *SMN1*-related proximal spinal muscular atrophy (SMA).

This difference would appear to be due to "particular attention by patients to self-isolation and hygiene measures", as well as to "actions taken by the neuromuscular patient associations and FILNEMUS", according to the conclusions of this national study.
Pisella LI et al. Orphanet J Rare Dis. 2021 Oct.

Similar vaccine response

▪ An American study of non-mobile patients with neuromuscular disease showed that, despite low muscle weight, the levels of antibodies produced in response to the COVID-19 vaccine was similar to that of the group of individuals without the disease who had been vaccinated.
Demonbreun AR et al. Neuromuscul Disord. 2022 Jan.

Clinical trials

Clinical trials are used to evaluate the effects of a potential treatment (a drug candidate, a medical device, etc.) in a disease, to make sure it is well tolerated and effective in this disease.

Did you know?

The 4 phases of a clinical trial

The candidate medicine is assessed over the course of successive trials, corresponding to different phases: I, II, III and IV.

- **Phase I: Safety/tolerability**

A candidate medicine is tested for the first time on a small group of individuals (often healthy volunteers), to assess its safety/tolerability and its distribution throughout the body (pharmacokinetics).

- **Phase II: Optimum dose/Effect**

Phase II, conducted on a homogeneous group of volunteers with the disease, studies the safety and efficacy of the product and determines the optimum dose to be used.

- **Phase III: Therapeutic efficacy**

Phase III is conducted on a larger number of participants who have the disease, in order to clarify the product's therapeutic efficacy compared to an existing treatment or a placebo. At the end of this trial, the medicine may obtain marketing authorisation.

- **Phase IV: Pharmacovigilance**

The goal of phase IV, which is conducted after the medicine has been brought to market, is to fine-tune knowledge of the product and to identify any serious and/or unexpected side effects due to its administration.

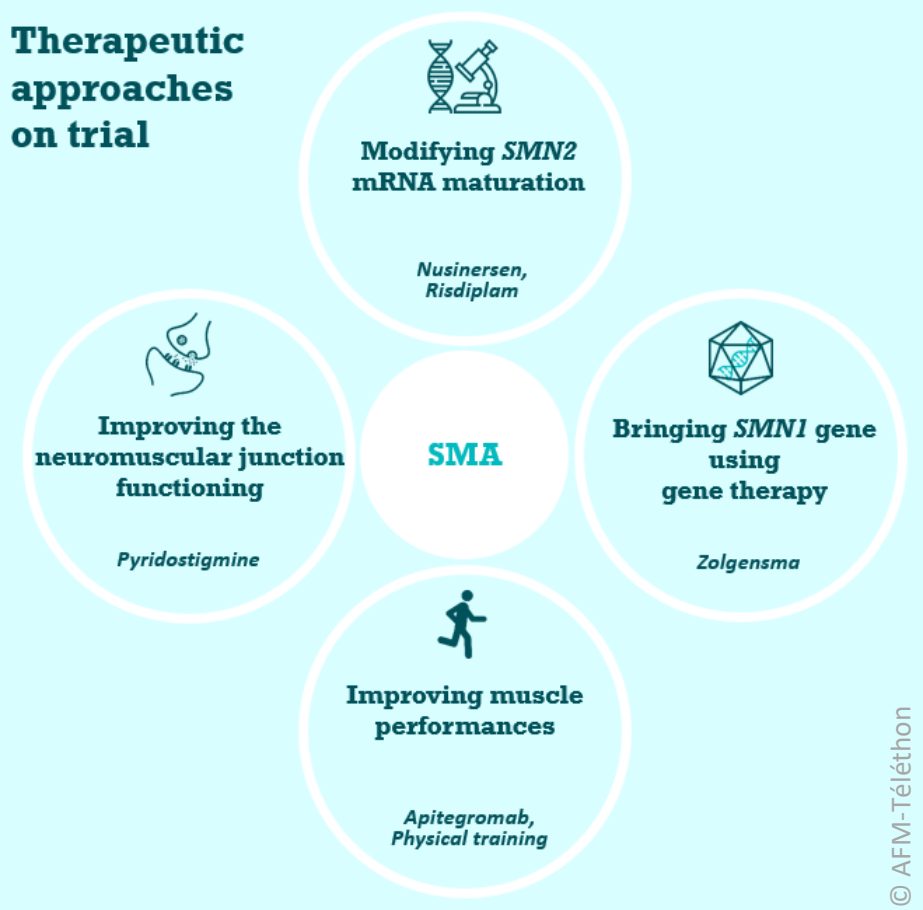
Multiple therapeutic strategies

Several therapeutic strategies, at different stages of development, are being investigated in *SMN1*-related proximal spinal muscular atrophy.

- The goal of certain therapeutic strategies is to increase the quantity of functional SMN protein:

- by modifying *SMN2* messenger RNA maturation to promote the inclusion of the missing exon 7,
- by providing the *SMN1* gene using gene therapy…

- Others aim to protect the motor neuron, to improve neuromuscular junction functioning, muscle performance, therapeutic management, etc.



Clinical trials in France

TRIAL TITLE Participants	THERAPEUTIC APPROACH	PRECLINICAL RESEARCH / CLINICAL DEVELOPMENT	REGULATORY ASPECT
SHINE trial	Gene therapy: Oligonucleotide targeting *SMN2*	**Nusinersen (Spinraza®)** (recruitment completed)	• European marketing authorisation June 2017 • Reimbursed April 2019
DEVOTE trial and extension phase	Gene therapy: Oligonucleotide targeting *SMN2*	**Nusinersen (Spinraza®)** (Recruitment underway)	
SMART trial	Gene therapy: AAV9-*SMN1*	**Onasemnogene abeparvovec-xioi (Zolgensma®)** (Recruitment underway)	• European marketing authorisation May 2020 • cohort Temporary Authorisation for Use (ATU) May 2020 • Post-ATU 2021
Long-term follow-up study	Gene therapy: AAV9-*SMN1*	**Onasemnogene abeparvovec-xioi (Zolgensma®)** (Recruitment completed)	
SUNFISH trial	Pharmacology: Small drug molecule targeting *SMN2*	**Risdiplam** (Recruitment completed)	• European marketing authorisation March 2021 • Reimbursed April 2022
FIREFISH trial	Pharmacology: Small drug molecule targeting *SMN2*	**Risdiplam** (Recruitment completed)	
JEWELFISH trial	Pharmacology: Small drug molecule targeting *SMN2*	**Risdiplam** (Recruitment completed)	

Nusinersen (Spinraza®)

Nusinersen (Spinraza®)

Worldwide

- **More than 11,000 patients treated as of 31 December 2020**
- **Available in more than 50 countries, including in Europe**

In France

- **Prescribed in specialist neuromuscular disease consultations**
- **Reimbursed for SMA I, II and III**

Method of administration

- **Regular injections intrathecally, between 2 lumbar vertebrae into the cerebrospinal fluid (at hospital)**

Antisense oligonucleotide

Nusinersen (Spinraza®), the first treatment authorised for SMA, is an antisense oligonucleotide developed with the aim of increasing the production of functional SMN protein **by acting on the maturation (splicing) of the *SMN2* gene**.

▪ Since antisense oligonucleotides do not cross the barrier between the circulating blood and the central nervous system (the blood-brain barrier), nusinersen is injected directly into the cerebrospinal fluid between two lumbar vertebrae, intrathecally (i.e. by lumbar puncture), so that it can reach the spinal cord and the brain.

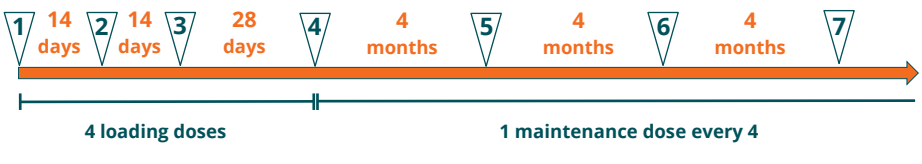
*An **antisense oligonucleotide (ASO)** is a DNA fragment, generally synthesised in a laboratory, that binds specifically to a natural messenger RNA (the antisense oligonucleotide sequence is complementary to that of the messenger RNA). Thus, it can modify the messenger RNA (exon skipping or incorporation) at a specific location by intervening at its maturation stage (splicing).*

***Splicing** is one of the steps in protein production. In the first step, transcription, the gene message is "transcribed" into pre-messenger RNA (a bit like a photocopy of the part of the DNA carrying the gene). In the second step, namely "splicing", the messenger RNA is spliced: certain parts (the introns) are cut and the remaining pieces (the exons) are recombined into a single mature messenger RNA strand that contains only the information needed to guide protein synthesis.*

The blood-brain barrier

The blood-brain barrier separates the central nervous system (brain and spinal cord) from the rest of the body. It is composed, essentially, of cells that line the inside of the small blood vessels (or capillaries) in the brain, closely connected to each other. The brain capillaries themselves are wrapped in nerve cell extensions (astrocytes) that participate in the blood-brain barrier.
This barrier plays a protective role with respect to the central nervous system. It allows certain useful compounds, such as glucose, to pass into the brain and the spinal cord. Conversely, it limits or prevents the passage of microorganisms, toxic substances and numerous medicines.

▪ Nusinersen, which is used in the treatment of SMA, allows the expression of the SMN protein in the motor neurons, with a real clinical benefit, but of varying significance depending on SMA type and age at start of treatment.



Frequency of administration of nusinersen
Treatment with nusinersen involves: 4 loading doses at days 0, 14, 28 and 63. A maintenance dose must then be administered every 4 months.

In France, a treatment reimbursed for SMA type I, II and III

Developed by Ionis Pharmaceuticals and Biogen, nusinersen (Spinraza®) obtained **marketing authorisation (MA)** in the United States in December 2016, and in Europe in June 2017, following the positive results obtained in the first clinical trials (open-label phase II, then phase III ENDEAR and CHERISH trials).

▪ In France, nusinersen is prescribed in specialist neuromuscular disease consultations after an opinion from an MDT meeting (a national multidisciplinary team consultation meeting). It is reimbursed for patients with SMA type I, II and III.

WEB http://circulaire.legifrance.gouv.fr/pdf/2019/04/cir_44554.pdf

Ongoing trials

In parallel, several clinical trials with nusinersen are proceeding, to continue to assess its effects according to SMA type, age at start of treatment, treatment duration, etc., with Biogen as sponsor.

SHINE trial

The SHINE trial is an open-label extension phase of the ENDEAR trial (among **infants** with SMA) and CHERISH trial (among **children** with SMA). Its goal is to assess the long-term tolerability and safety of nusinersen.

▪ The latest reported results regarding the SHINE trial indicated that nusinersen improves motor function, and even leads to stabilisation of the disease, in infants, children and young adults alike, receiving continuous treatment (some over a period of up to six-and-a-half years).

Biogen, Press release of 18 May 2020

SHINE trial

Phase III
Efficacy

In France and abroad

292 participants

Recruitment completed

5 years of follow up

Nov. 2015 – Aug. 2023

NCT02594124

NURTURE trial

The goal of the NURTURE trial is to assess whether the administration of nusinersen during the first few weeks of life can prevent or lessen the severity of the disease among **25 newborns who have** genetically-confirmed **SMA** but do not yet present symptoms (**presymptomatic**), aged less than 6 weeks and likely to develop SMA type I or II.

To date, this is the longest trial studying the effects of a treatment among presymptomatic newborns with SMA.

▪ Interim results obtained in children treated for up to 5.7 years with nusinersen have shown that their motor function continues to improve. A very large majority are able to walk with assistance. Based on these results, this trial that is international (but not being conducted in France), with an initial planned duration of 5 years, has been extended to a total duration of 8 years

Biogen, Press release of 14 March 2022

Phase II
Dose/effect

NURTURE trial: phase II trial among presymptomatic infants

Abroad (outside France)

25 participants (less than 6 weeks)

Recruitment completed

8 years of follow up

May 2015 – Jan. 2025

NCT02386553

DEVOTE trial

The goal of the DEVOTE trial is to assess whether **a higher dose of nusinersen** than the dose currently used would be well tolerated and more efficient. Currently, nusinersen is administered at a dose of 12 mg per intrathecal injection. While this helps to improve motor skills and increase patient life expectancy, this dose does not always provide a significant improvement.

▪ The DEVOTE trial consists of three phases lasting 10 months each:

- the first, open-label, assesses the safety of 28 mg of nusinersen, i.e. slightly more than twice the dose used up to now;
- the second, double-blind, compares two groups receiving nusinersen: one at a high dose (50 mg then 28 mg) and the other at the currently authorised dose (12 mg);
- the third, open-label, tests the highest dose (50 mg then 28 mg) among participants who have previously received a dose of 12 mg for at least one year.

DEVOTE trial

1st phase

- **Nusinersen (28 mg)**
- **Open-label**
- **Tolerability and safety**

2nd phase

versus

- **Comparison high dose (50 mg then 28 mg) versus current dose (12 mg)**
- **Double blind, randomised**
- **Efficacy**

3rd phase

- **High dose (50 mg then 28 mg)**
- **Open-label**
- **After at least 1 year of treatment at the current dose (12 mg)**

▪ For this trial, 172 participants with SMA of all types are currently being recruited in several countries (Germany, Canada, Colombia, Korea, Spain, Estonia, United States, Greece, Hungary, Ireland, Italy, Japan, Latvia, Poland, Russia, Taiwan), including France.

▪ Results for the first phase were presented at the annual American Academy of Neurology (AAN) annual meeting, which took place online from 17 to 22 April 2021: the treatment is well tolerated at a dose of 20 mg, over a follow-up period of up to 5 months.

Biogen, Press release of 19 April 2021

DEVOTE trial: phase II/III trial with a high dose of nusinersen

Phase II
Dose/effect

Phase III
Efficacy

In France and abroad

172 participants (all ages)

Ongoing recruitment

10 months of follow up

Mar. 2020 – Jul. 2023

NCT04089566

▪ An extension phase will assess the effects of the highest doses of nusinersen in the longer term.

Extension phase of DEVOTE trial

Phase III
Efficacy

In France and abroad

172 participants (all ages)

Ongoing recruitment

3 years of follow up

Apr. 2021 – May 2026

NCT04729907

New results with nusinersen

▪ Different studies conducted on the progression of diseases treated with nusinersen show a tendency for improvement compared to the natural progression of the disease (without treatment).
A review relating to 400 published articles reports that in all groups, patients improved for at least one motor function. However, these results should be treated with care, since very few studies have objectively compared the progression of treated versus untreated patients.
Coratti G et al. Orphanet J Rare Dis. 2021 Oct

▪ The assessment of bulbar involvement, such as deglutition or speech disorders, has not yet been well described in patients taking nusinersen. A German study recently studied the effects of nusinersen on these symptoms, but showed neither an improvement nor a deterioration after 6 and 14 months of treatment, among 23 patients.
Brakemeier S et al. Brain Sci. 2021 Sep.

▪ A British study among 24 children with SMA type I has revealed the little impact that nusinersen has on difficulty eating, using a functional scale tailored to children, exploring the impact of difficulty swallowing on food intake via the mouth (Paediatric Functional Oral Intake Scale).
Weststrate H et al. Dev Med Child Neurol. 2022 Feb.

▪ A review of the different studies conducted among 428 patients with SMA over 12 years of age has shown a significant improvement, after 10 and 14

months of treatment, in motor function. In contrast, the 6-minute walk test and lung function did not improve.
Gavriilaki M et al. Neurotherapeutics. 2022 Feb.

- A study relating to the efficacy of nusinersen over 12 and 24 months of treatment in patients with SMA type II and III showed a moderate improvement in motor function after 2 years of treatment.
Pane M et al. Ann Clin Transl Neurol. 2022 Mar.

- An assessment of 144 children and adults with SMA type III taking nusinersen showed that, for the 100 patients for whom an assessment was available after 12 months of treatment, motor function showed significant improvement only in the paediatric population. In contrast, the 6-minute walk test did not show a change.
Pera MC at al. Ann Clin Transl Neurol. 2021 Aug.

- A study assessing quality of life using a validated self-administered questionnaire among 78 patients (7 with SMA type II, 69 with SMA type III and 2 with SMA type IV) showed a significant improvement for 7 of the 9 items after 14 months of treatment.
Bonanno S et al. J Neurol. 2022 Jun.

Ongoing observational studies

Observational studies with nusinersen are being conducted among children or adolescents, or among adults, with SMA.

- A prospective observational study of the effects of nusinersen in routine care, the sponsor of which is Washington University School of Medicine, is currently in the process of recruiting adults with SMA type II or III in North America.

SAS study

In the United States and Canada

48 participants (18 to 70 years)

Recruitment completed

30 months of follow up

Aug. 2018 – Jan. 2024

NCT03709784

- An observational study assessing the effects of nusinersen on the motor function of mobile and non-mobile adults is in progress in the United States, with Northwell Health as sponsor.

Nusinersen study among adults with SMA type II and III

In the United States

12 participants (18 to 60 years)

Recruitment completed

2 years of follow up

Apr. 2019 – Jan. 2023

NCT03878030

▪ Another American study of nusinersen in mobile adults, the sponsor of which is Ohio State University, is in progress.

Nusinersen study among adults with SMA who are mobile

In the United States

15 participants (18 to 60

Trial ended, data undergoing analysis

22 months of follow up

Oct. 2018 – Jun. 2021

NCT04591678

▪ In France, the NusiMFM study, conducted by the Hospices Civils de Lyon, will be using motor function measure (MFM) to follow up motor function progression in children with SMA type I and II being treated with nusinersen.

NusiMFM study

In France

60 participants (2 to 6

Recruitment underway

1 year of follow up

Jan. 2021 – Mar. 2023

NCT04602195

▪ In a German study, multispectral opto-acoustic tomography (MSOT) and magnetic resonance imaging (MRI) are used to characterise the molecular composition of muscle tissue non-invasively and to assess response to nusinersen in SMA type III. The sponsor is the University of Erlangen-Nürnberg Medical School.

Guidelines for restarting nusinersen in case of treatment interruption

▪ International guidelines have recently been published regarding the restarting of nusinersen after treatment interruption. The number of doses of nusinersen injected at close intervals after restarting the treatment depends on the duration of interruption.

MacCannell D et al. CNS Drugs. 2022 Feb.

Zolgensma® (onasemnogene abeparvovec or AVXS-101)

Onasemnogene abeparvovec (Zolgensma®)

Worldwide

- **More than 1800 patients treated as of 14 March 2022**
- **Available in more than 40 countries**
- **In Europe: Conditional Marketing Authorisation**

In France

- **Cohort ATU (Temporary Authorisation for Use)**
- **Favourable opinion regarding reimbursement: SMA types I and II, or presymptomatic with up to 3 copies of *SMN2***

Method of administration

- **A single injection by intravenous infusion (at hospital)**

A gene therapy product

Zolgensma® or onasemnogene abeparvovec (AVXS-101) is a gene therapy treatment for *SMN1* gene-related proximal spinal muscular atrophy (SMA) that consists of **introducing the *SMN1* gene using an AAV vector** (adeno-associated virus). It was initially developed by the American pharmaceutical company, AveXis, since acquired by Novartis.

Did you know?

A vector, a transportation method for delivering genetic material

A vector is a system that allows gene medicines to be transferred into the cells of a body. In order to have an effect, a gene medicine must enter the cell's nucleus, where the DNA is located. This gene medicine must therefore cross several biological barriers to reach first the cell (by crossing the vessels and the conjunctive tissues), then the inside of the cell (by crossing the plasma membrane delimiting the cell), then finally the nucleus (by crossing the nuclear membrane). To achieve this, the gene medicine is introduced into a vector that helps it to cross all these barriers. The vector can be either viral, or non-viral (plasmids, lipid vectors, etc.).

▪ The efficacy of this gene therapy was demonstrated for the first time in mice models with SMA, thanks to researchers at Généthon and the Institute of Myology. Généthon then granted, to AveXis, a licence to use the patents relating to the AAV9-SMN products, and its administration in vivo into the central nervous system, by intrathecal or intravenous route.

In Europe, a "conditional" marketing authorisation

▪ After having received marketing authorisation (MA) in the United States for the first time in May 2019, Zolgensma® obtained, in May 2020, **"conditional" European marketing authorisation**. This authorisation concerns only babies and young children weighing less than 21 kg, presenting SMA type I or carriers of a bi-allelic mutation of the *SMN1* gene and of a maximum of 3 copies of the *SMN2* gene.

The health authorities in each European country will now assess the therapeutic and economic benefit of the treatment, in order to finalise its marketing status in their country.

WEB www.ema.europa.eu/en/medicines/human/EPAR/zolgensma

Marketing authorisation *(MA) allows a new medicine to be marketed. It is issued in France by the ANSM (French National Agency for Medicines and Health Products Safety) or, at the European level, by the European Commission, after an opinion is issued by the European Medicines Agency. In order to obtain this marketing authorisation, the pharmaceutical company must provide scientific data from the different phases of development, in particular from clinical trials. The decision is made based on quality, safety and efficacy criteria.*

In France, a post-ATU mechanism…

▪ In France, Zolgensma® has been prescribed since 25 May 2020 in the context of a **cohort ATU (Temporary Authorisation for Use), then a post-ATU mechanism**. According to the information indicated in the protocol for therapeutic use (PTU) and the collection of information that accompanies it, this cohort ATU concerns children weighing less than 21 kg "with a clinical diagnosis of *SMN1*-related proximal spinal muscular atrophy (SMA) type I or with SMA with a bi-allelic mutation of the *SMN1* gene and up to 3 copies of the *SMN2* gene".

*In France, an **ATU (Temporary Authorisation for Use)** is a regulatory mechanism allowing the use of a medicine before its marketing authorisation is granted for a particular indication (a specific disease).*

▪ Zolgensma® is reserved for hospital use and is prescribed only after a favourable opinion is provided by a multidisciplinary team (MDT) consultation meeting from the FILNEMUS healthcare network.

… and an opinion from the HAS (French National Authority for Health) regarding reimbursement

▪ The HAS (French National Authority for Health) Transparency Commission published in December 2020:
- a **favourable opinion regarding reimbursement** for the treatment of patients with spinal muscular atrophy 5q (bi-allelic mutation of the *SMN1* gene), with a clinical diagnosis of **SMA type I and type II or presymptomatic with up to 3 copies of the *SMN2* gene, based on a French SMR (actual medical benefit) deemed "significant",**
- an **unfavourable opinion regarding reimbursement** for the treatment of patients with spinal muscular atrophy 5q (bi-allelic mutation of the *SMN1* gene) with a clinical diagnosis of **SMA type III**, a situation for which Zolgensma® has been attributed an **"insufficient" SMR (actual medical benefit), due to an amount of data deemed to be insufficient to date**.

▪ The HAS has, additionally, attributed an ASMR (improvement of medical benefit) level III, i.e. "moderate", to Zolgensma® for patients with SMA type I or those presymptomatic with a genetic diagnosis of SMA (bi-allelic mutation of the *SMN1* gene) and 1 or 2 copies of the *SMN2* gene.
Conversely, it has attributed an ASMR (improvement of medical benefit) **level V (no therapeutic progress)** for patients with SMA type II, or who are presymptomatic with a genetic diagnosis of SMA (bi-allelic mutation of the *SMN1* gene) and 3 copies of the *SMN2* gene.

▪ The opinion of the Transparency Commission notes as a reminder that **the decision to treat will be taken on a case-by-case basis** during multidisciplinary team consultation meetings organised at the national level by the FILNEMUS rare neuromuscular diseases healthcare network.
ZOLGENSMA (onasemnogene abeparvovec). HAS. Uploaded on 18 December 2020

Expanded access protocol to Zolgensma® in the United States

An expanded access protocol to Zolgensma® for patients with SMA who do not fulfil the enrolment criteria for trials currently in progress has been in existence since May 2019 in the United States.

Expanded access protocol to Zolgensma® for patients with SMA who have 1, 2 or 3 copies of the SMN2 gene

In the United States

All ages

Ongoing recruitment

Follow up not specified

Started in May 2019

NCT03955679

Ongoing trials

Other clinical trials are continuing to assess, worldwide, the effects of Zolgensma® for different types of SMA (I, II, presymptomatic stage, etc.), sponsored by Novartis Gene Therapies.

The START long-term follow-up study

The **very first gene therapy trial with Zolgensma®**, called the "START trial", was conducted in the United States from May 2014 to December 2017 in 15 infants with **SMA type I, aged less than 6 months and symptomatic**. In 2019, the publication of the results of this trial over a two-year period showed a 100% survival rate for the group treated with Zolgensma® (while this rate was 38% for the untreated group), and an improvement in motor function and motor development.

▪ This study, now called "Long-term follow up "START study", is being conducted to assess the safety and the treatment response duration over a 15 year period. A first set of results, after a 5-year follow up, has just been published, relating to 13 participants, 3 of which had received a low dose of Zolgensma® and 10 the therapeutic dose. Eight participants (one receiving a low dose and seven a therapeutic dose) reported having experienced serious adverse events (acute respiratory failure, pneumonia, dehydration, respiratory distress, bronchiolitis). However, these events were all considered not to be related to Zolgensma®.
All the participants are alive and a large majority (12 of the 13) do not require permanent ventilation. Two of the participants who received the therapeutic dose are able to stand up without assistance.
Mendell JR et al. JAMA Neurol. 2021 May.

Phase I
Safety/tolerability

START study

In the United States

13 participants

Recruitment completed

Up to 15 years of follow up

Sep. 2017 – Dec. 2033

NCT03421977

STR1VE trial

The STR1VE trial, a phase III open-label trial (with no placebo group), was conducted at 12 centres in the United States, between October 2017 and November 2019. It concerned 22 infants with SMA type I, presenting one or two copies of the *SMN2* gene and aged less than 6 months at the time they received a single injection of Zolgensma® intravenously, and were followed up until the age of 18 months.
This trial was designed to confirm, with a larger number of participants, the positive results of the very first Zolgensma® trial, the START trial, which had been conducted among 15 participants with SMA type I, aged less than 6 months at the time they received the injection of the product, and that the American regulatory authorities had used to support the marketing authorisation of the medicine in the United States.

- The results of the STR1VE trial published in April 2021 showed that Zolgensma® was well tolerated. At the age of 14 months, 91% of the participants did not require continuous ventilation and 59% were capable of sitting up alone for at least 30 seconds at the age of 18 months.
Day JW et al. Lancet Neurol. 2021 (Avr).20(4):284-293.

STR1VE-EU trial

The STR1VE-EU trial is a European trial that started, in France, in March 2019 at a single centre: the I-Motion Institute at the Trousseau Hospital (Paris). It concerns infants with **SMA type I**, and its goal was to assess the effects (safety and efficacy) of a single **intravenous infusion** of Zolgensma®.
It was conducted in parallel with the STR1VE trial, which is assessing Zolgensma® in the United States in accordance with the same protocol.
As with the American STR1VE trial, the results of which were published in April 2021, Zolgensma® was well tolerated during the European STR1VE-EU trial, and its beneficial effects are confirmed in SMA type I: at the age of 18 months, 44% of infants were capable of sitting up alone for at least 10 seconds. Almost all the participants (97%) did not need continuous ventilation at 14 months.
Mercuri E et al. Lancet Neurol. 2021 Oct.

STEER trial, with intrathecal administration

In this trial, 125 participants with SMA type II, aged 2 to 18 years, able to sit up but never having walked, and treatment naïve for all treatments, will be enrolled. Randomised, versus a dummy procedure (equivalent to a placebo), this trial will assess the tolerability, the safety and the efficacy of an intrathecal injection to the lower back, as with a lumbar puncture, of Zolgensma® (onasemnogene abeparvovec). To date, this product has only been administered intravenously.
Novartis, Press release dated 3 August 2021.

STEER trial

Phase III
Efficacy

In the United States and Singapore

125 participants (2 to 17 years)

Ongoing recruitment

1 year of follow up

Feb. 2022 – Oct. 2024

NCT05089656

SPR1NT trial

The phase III SPR1NT trial relates to infants with SMA aged **less than 6 months who do not yet have any disease symptoms**. It is being conducted abroad (Australia, Germany, Belgium, Canada, Korea, Spain, United States, Israel, Italy, Japan, United Kingdom, Taiwan), but not in France.

- Preliminary results showed that infants with SMA who are presymptomatic and treated with Zolgensma® shortly after birth, show motor development that is appropriate for their age, including sitting up, standing up and walking. None of them required ventilatory assistance.
Novartis, Press release of 15 March 2021

Phase III
Efficacy

Phase III open-label SPR1NT trial among presymptomatic infants with 2 or 3 copies of the *SMN2* gene

Abroad (outside France)

30 participants (less than 6 weeks)

Trial ended, data undergoing analysis

Follow up, up to 3 years of age

Apr. 2018 – Jun. 2021

NCT03505099

SMART trial

The phase III, open-label SMART trial started in September 2021. The objective of this trial lasting one year is to assess the safety, tolerability and efficacy of a single intravenous infusion of Zolgensma® among 24 participants with SMA, weighing more than 8.5 kg and less than 21 kg.
In France, the involvement of participants is validated during a national multidisciplinary team (MDT) consultation meeting from the FILNEMUS rare neuromuscular diseases healthcare network.

Phase III
Efficacy

Phase III open-label SMART trial among infants weighing more than 8.5 kg and less than 21 kg

In France and abroad

24 participants (less than 17

Ongoing recruitment

1 year of follow up

Sep. 2021 – Aug. 2023

NCT04851873

Long-term follow-up study

A long-term follow-up study (up to 15 years), of patients with SMA type I, II or III who have been treated with Zolgensma® as part of a clinical trial (other than the START trial), started in February 2020. France is participating in this international study.

Long-term follow-up study of Zolgensma® in SMA type I, II or III

In France and abroad

308 participants (all ages)

Ongoing ecruitment

Up to 15 years of follow up

Feb. 2020 – Dec. 2035

NCT04042025

Safety profile

An initial exhaustive analysis of the results of Zolgensma® has shown that the risks associated with this gene therapy product, if any exist, can be anticipated or managed, sometimes via a medical procedure. These conclusions were published by American clinicians, who reviewed all the preclinical, clinical and post-marketing data obtained up to 12 November 2020: from mice, to monkeys, to humans, with more than 760 treated SMA patients.

▪ However, serious transient side effects did appear in very rare cases: hepatic impairment, thrombotic microangiopathy, cardiac problems, etc. Increased monitoring and systematic preventive measures, such as temporary use of corticosteroids to prevent hepatic involvement, have now been put in place to limit these. If necessary, specific treatments are initiated.

Day JW et al. Drug Saf. 2021 Oct.

Risdiplam (Evrysdi® or RO7034067)

Risdiplam (Evrysdi®)

Worldwide	In France	Method of administration
		
• More than 5000 patients treated as of 31 May 2022 • Available in more than 81 countries, including in Europe	• SMA I, II and III at age over 2 months • Reimbursed, prescribed at hospital and dispensed in pharmacy	• Taken orally or by feeding tube once per day (at home)

A small drug molecule administered orally

Developed by Hoffmann-La Roche and PTC Therapeutics in collaboration with the SMA Foundation, Risdiplam (Evrysdi® or RO7034067) is a small drug molecule that **modulates the maturation of *SMN2* messenger RNA to promote the inclusion of the missing exon 7**. The inclusion of this exon 7 helps to synthesise a complete and functional SMN protein.

*Genes are structured as alternating coding sequences, the **exons**, and non-coding sequences, the introns. The exons are the parts of the gene that are used by the cell machinery as an assembly guide for protein production.*

Four ongoing trials

▪ Four trials being conducted by the sponsor, Hoffmann-La Roche, with risdiplam, are currently in progress worldwide in SMA:
- the **SUNFISH trial** in SMA type II or III,
- the **FIREFISH trial** in SMA type I,
- the **JEWELFISH trial** in patients 6 months to 60 years of age who have already been treated with nusinersen (Spinraza®), olesoxime or onasemnogene abeparvovec (Zolgensma®)
- the **RAINBOWFISH trial** in presymptomatic infants aged less than 6 weeks and diagnosed with SMA using a genetic test.

Marketing authorisation obtained in Europe

▪ In March 2021, risdiplam (Evrysdi®) obtained European marketing authorisation for "patients aged more than two months, with a clinical diagnosis of SMA type I, type II or type III, or with 1 to 4 copies of the *SMN2* gene".
Roche. Press release of 30 March 2021

In France, risdiplam reimbursed and in pharmacy

▪ Since April 2022, risdiplam has been marketed in France for patients with SMA type I, II and III, and aged more than 2 months.

▪ Risdiplam is now officially one of the medicines that are reimbursable in SMA, and is becoming available outside of hospitals, in retail pharmacies (although prescription remains hospital-based). A publication in the Official Journal (of the French Republic) dated 12 April 2022 adds risdiplam to the list of proprietary medicinal products that are reimbursable in the treatment of certain forms of *SMN1*-related proximal spinal muscular atrophy.

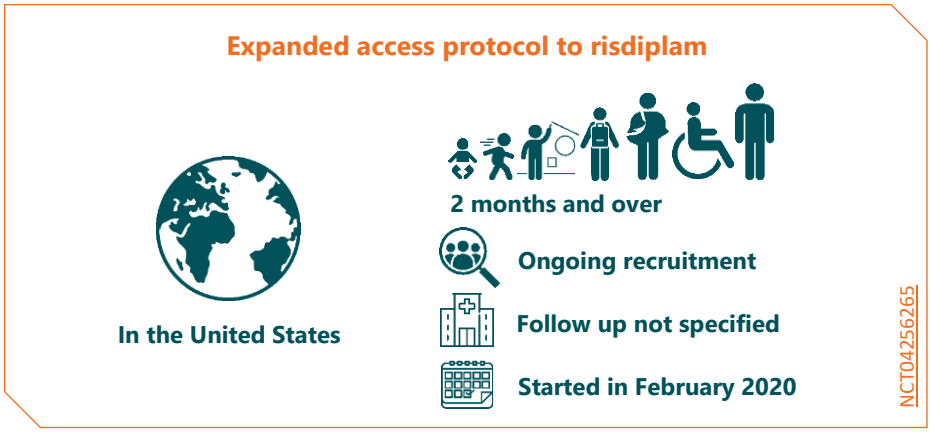
▪ The monitoring of these potential adverse effects is continuing, and at the same time, clinical trials are continuing to refine the assessment of its

efficacy. To date, the only therapeutic indication eligible for reimbursement of risdiplam by the French health insurance system is "the treatment of spinal muscular atrophy (SMA) 5q among patients aged 2 months or more with a clinical diagnosis of SMA type I, type II and type III". The HAS (French National Authority for Health) recommends that this treatment may be used as a first-line treatment:
- in patients with SMA type I who present symptoms of this condition, in the same way as Spinraza® and Zolgensma®,
- in patients with SMA type II and III, in the same way as Spinraza®.
The prescription of risdiplam continues to be restricted to neurologists or paediatric neurologists at reference centres or centres of expertise for neuromuscular diseases from the FILNEMUS network.

Order dated 6 April 2022 modifying the list of proprietary medicinal products reimbursable to individuals covered by the French social security system, JORF No. 0086 dated 12 April 2022
Order dated 6 April 2022 modifying the list of proprietary medicinal products approved for use by healthcare institutions and various public services, JORF No. 0086 dated 12 April 2022
Opinion relating to the prices of proprietary medicinal products, JORF No. 0086 dated 12 April 2022

Expanded access protocol to risdiplam in the United States

▪ An expanded access protocol to risdiplam is currently in place in the United States to allow children with SMA type I and II to benefit from the treatment. The sponsor is Genentech, Inc.



SUNFISH trial

The SUNFISH trial is assessing the effects of risdiplam in 231 patients with **SMA type II and III, aged from 2 to 25 years**.
▪ This phase II, controlled, double-blind trial is being conducted in several countries worldwide, including France. It consists of two parts:
- a first part lasting 3 months to test tolerability and identify the optimum dose in mobile and non-mobile participants;
- a second part lasting 2 years, whose goal is to assess the safety and efficacy of this optimum dose (compared to a placebo) in non-mobile participants.
▪ Results obtained at the end of the first part showed the **good tolerability of risdiplam**, which, after 2 years of treatment, significantly improved the motor functions of participants.

▪ Results from the second part of the trial showed **an improvement or stabilisation in motor function** for patients with SMA type II and III after two years taking risdiplam, compared to those receiving the placebo.
Roche, Press release of 16 March 2021
PTC Therapeutics, Press release of 16 March 2021

Phase II
Dose/effect

Phase III
Efficacy

SUNFISH trial: phase II/III trial in SMA type II or III

In France and abroad

231 participants (2 to 25

Recruitment completed

2 years of follow up

Oct. 2016 – Sep. 2023

NCT02908685

FIREFISH trial

The FIREFISH trial is assessing the safety, the tolerability, the "journey" through the body (pharmacokinetics) and the efficacy of different doses of risdiplam in 62 infants with **SMA type I, aged 1 to 7 months**. It is an international open-label trial that is also being conducted in France, in two parts: the first part lasted one month, showing that risdiplam is well tolerated, and the second part lasts two years, assessing its efficacy.

▪ Initial results relating to 41 infants showed that 29% of patients were able to sit up without assistance for at least 5 seconds (an ability that has never been acquired without treatment). Additionally, the patients presented motor scores and a change of these motor scores in one year that are significantly higher than the historical cohorts of untreated patients with SMA type I. Finally, 85% of patients alive at one year did not require ventilation (versus 42% in the natural history cohorts). The most frequently described adverse events are essentially respiratory (bronchiolitis, pneumonia, respiratory failure).

▪ Preliminary results announced by the pharmaceutical company indicated that these improvements are confirmed **after two years of treatment**:
- the life expectancy of participants has increased,
- the need for permanent ventilation has decreased,
- 61% of infants are able to sit up without assistance for 5 seconds,
- 63% are able to keep their head straight,
- 15% are able to remain standing with support.

Darras BT et al. N Engl J Med. 2021 Jul 29;385(5):427-435.
PTC Therapeutics. Press release of 15 April 2021

Phase II
Dose/effect

Phase III
Efficacy

FIREFISH trial: phase II/III trial in SMA type I

In France and abroad

62 participants (1 to 7 months)

Recruitment completed

2 years of follow up

Dec. 2016 – Nov. 2023

NCT02913482

JEWELFISH trial

The JEWELFISH trial is an open-label trial lasting two years among children or adults with **SMA aged 6 months to 60 years, who have already been treated with onasemnogene abeparvovec (Zolgensma®)**. After 2 years, the participants will be able to receive risdiplam during the extension to the open-label trial (OLE trial).

- Initial results have shown a rapid and sustained increase in the quantity of SMN protein in participants after one year of treatment.

Roche, Press release of 12 June 2020

Phase II
Dose/effect

JEWELFISH trial

In France and abroad

174 participants (6 months to 60

Recruitment completed

2 years of follow up

Mar. 2017 – Dec. 2024

NCT03032172

RAINBOWFISH trial

The RAINBOWFISH trial is a multicentre, open-label clinical study, in **presymptomatic newborns and infants, aged less than 6 weeks**.

Its objective is to assess the safety, efficacy and the "journey" through the body of risdiplam in newborns and infants diagnosed as having SMA (genetic test), but who are asymptomatic.

- Initial results at one year have shown that the majority of presymptomatic babies treated with risdiplam have achieved key stages in their development, such as sitting up or standing.

Roche, Press release of 31 May 2022

Phase II
Dose/effect

RAINBOWFISH trial

Abroad (outside France)

25 participants (up to 6 weeks)

Ongoing recruitment

5 years of follow up

Apr. 2019 – Jan. 2029

NCT03779334

Trials combining two treatments

RESPOND study

The RESPOND study is assessing the effects of nusinersen (Spinraza®) in very young children (3 to 36 months) with SMA that has already been treated with onasemnogene abeparvovec (Zolgensma®) with insufficiently satisfactory effects. Started in January 2021, it is being conducted in Germany, Spain, the United States and Italy, but not in France.

- Together, the two treatments may better target all the body's motor neurons, to increase the production of SMN protein.

Phase IV
Pharmacovigilance

RESPOND trial

Abroad (outside France)

60 participants (2 to 36 months)

Recruitment underway

2 years of follow up

Jan. 2021 – Sep. 2024

NCT04488133

MANATEE trial

Another clinical trial called MANATEE, which aims to test the effects of an anti-myostatin, GYM329 (RO7204239) combined with Evrysdi® in SMA, should start in 2022. In contrast to Evrysdi®, which acts on the production of SMN protein, GYM329 targets the muscles directly, by blocking myostatin, a protein that naturally inhibits muscle growth. Together, these two treatments could improve muscle function and muscle strength.

Phase II
Dose/effect

Phase III
Efficacy

MANATEE trial

In Belgium and Poland

180 participants (2 to 10 years)

Recruitment underway

4.5 years of follow

Jun. 2022 – Dec. 2026

NCT05115110

RESILIENT trial, in preparation

Phase III
Efficacy

Another trial with an anti-myostatin, taldefgrobep alfa, is in preparation, among 225 patients with SMA that is already being treated with Spinraza®, Zolgensma® or Evrysdi®, in the United States.
Clinicaltrials.gov: NCT05337553

ASCEND trial, in preparation

Phase III
Efficacy

A phase III trial is in preparation, to assess the effects of a higher dose of Spinraza® (nusinersen) than the one currently being used (dose assessed in the DEVOTE trial), in patients with a late-onset form of SMA being treated with Évrysdi® (risdiplam). This trial, with a planned duration of 2.5 years, should involve 135 non-mobile patients.
Biogen, Press release of 15 September 2021

Other clinical trials

The curtain comes down on branaplam (ou LMI070)

Branaplam (or LMI070) is, like risdiplam, a small drug molecule that acts on the maturation (splicing) of the *SMN2* gene.

- A trial conducted by Novartis had started among infants with SMA type I.
- In the last few years, three innovative treatments (Spinraza®, Zolgensma® and Evrysdi®) have received marketing authorisation in SMA. It is in this encouraging therapeutic context that Novartis announced, in July 2021, they were **stopping the development of branaplam**.

SMA Europe. Press release of 23 July 2021

Improving neuromuscular junction functioning

In SMA, and more specifically in SMA type III, there are structural and functional abnormalities in the neuromuscular junction.

Did you know?

The neuromuscular junction

The neuromuscular junction is an area of communication (synapse) between the nerve, through which the contraction signal (nerve impulse) arrives, and the muscle, which contracts as a result of the nerve impulse.

Several treatments acting on the neuromuscular junction, and already used in other neuromuscular diseases, are being studied in SMA. They may be able to correct neuromuscular junction abnormalities and motor neuron degeneration.

Pyridostigmine

Pyridostigmine is an anticholinesterase, i.e. it inhibits the action of acetylcholinesterase, the enzyme that degrades acetylcholine in the neuromuscular junction. By preventing acetylcholine degradation, pyridostigmine improves the transmission of nerve impulses between the nerve and the muscle.

It has been assessed by a phase II trial (sponsor: UMC Utrecht) in **SMA type II, III or IV** over a period of two months. The trial has ended, and the data are undergoing analysis.

SPACE trial: phase II trial in SMA type II, III or IV

Phase II
Dose/effect

In the Netherlands

39 participants (12 years and

Trial ended, data undergoing analysis

2 months of follow up

Dec. 2015 – Jan. 2018

NCT02941328

Improving muscle performance

Apitegromab (or SRK-015)

Unlike the majority of treatments developed in SMA that act on the production of SMN protein, SRK-015 targets the muscle directly: it blocks the activity of myostatin, a protein that naturally inhibits muscle growth.

Thus, it could act as a treatment to complement the medicines that increase SMN protein expression (such as Spinraza®), to improve muscle development and strength.

- Developed by Scholar Rock, SRK-015 has received "orphan medicine" designation by the American health authorities (the FDA or Food and Drug Administration).
- Work conducted in mouse models of SMA has shown that SRK-015 improves their muscle strength. It also increases body mass considerably in monkeys.
- Another study in rats and monkeys has shown that the product has a low toxicity.

Welsh BT et al. Int J Toxicol. 2021 Jul-Aug.

Phase I
Safety/tolerability

- Scholar Rock has successfully conducted a phase I trial of SRK-015 in volunteers without the disease. They tolerated the product well, with assessment occurring at different doses.

Barrett D et al. Adv Ther. 2021 May.

- The phase II TOPAZ trial started in April 2019 in the United States and Europe (but not in France), among 58 patients with SMA type II or III, aged between 2 and 21 years. They are receiving a dose of SRK-015 intravenously once every 4 weeks for a period of one year. Its safety and efficacy are being studied using 3 cohorts:

- the first involving 23 participants aged 7 to 21 years, with **SMA type III, mobile**, taking or not taking a treatment to increase SMN production (nusinersen), and being treated with 20 mg/kg of SRK-015;
- the second involving 15 participants aged 8 to 19 years, with **SMA type II or type III, non-mobile**, taking nusinersen and also treated with 20 mg/kg of SRK-015;
- the third involving 20 children aged 2 to 6 years, with **SMA type II**, who started to receive a nusinersen treatment before the age of 5 years, to assess, double-blind, 2 doses of SRK-015 (2 mg/kg or 20 mg/kg).

- Positive preliminary results for this trial at 6 months were announced by a press release: **motor function was improved in all three cohorts**. In the third cohort, the highest dose was the most efficacious. In addition, the treatment was well tolerated by all participants. This trial should end in April 2023.

Scholar Rock, Press release of 27 October 2020

Phase II
Dose/effect

TOPAZ trial

In the United States, Spain, Italy and the Netherlands

58 participants (2 to 21 years)

Recruitment completed

1 year of follow up

Apr. 2019 – Apr. 2024

NCT03921528

Physical training

Physical training may improve motor function in *SMN1*-related proximal spinal muscular atrophy, by combating muscle and cardiovascular deconditioning on exertion, and by strengthening the functional motor units not affected by the disease.

▪ A French trial, the sponsor of which is the APHP (Paris Network of Public Hospitals), has assessed the effects of swimming pool training in SMA type II and III. The trial has now ended, and the data are undergoing analysis.

ExerASI: physical training in SMA type II and III

In France

19 participants (5 to 10

Trial ended, data undergoing analysis

18 to 36 months of follow up

Mar. 2014 – Apr. 2020

NCT02061189

▪ A trial is being conducted in the United States to assess the effects of physical training on oxidative capacity and exercise tolerance. The sponsor is Columbia University.

Physical training trial in SMA type III

In the United States

42 participants (8 to 55 years)

Trial ended, data undergoing analysis

6 months of follow up

Nov. 2016 – Jan. 2021

NCT02895789

Clinical studies in *SMN1* gene-related proximal spinal muscular atrophy

Two types of **observational clinical study**:
- **longitudinal studies**, describing the progression of the disease over time (for example, a natural history protocol).
- **cross-sectional studies**, describing how the disease manifests in a group/population of patients at a specific moment in time,

Long-term longitudinal studies

Three longitudinal studies are in progress in the United States or China, in SMA type I, II and III.

- The SPOT SMA study, an American longitudinal observational study, is in the process of recruiting infants or children who are presymptomatic or recently diagnosed, with SMA type I, II or III, as well as parents or brothers/sisters without the condition.

SPOT SMA study in SMA type I, II and III

In the United States

1000 participants (all ages)

Ongoing recruitment

10 years of follow up

Feb. 2016 – Mar. 2022

NCT02831296

- A long-term cohort study in SMA type I, II and III is in the process of recruiting in China, in order to monitor, over the long-term, the clinical course of the disease, and also motor and lung function, food intake, growth, development, etc.

Long-term cohort study in SMA type I, II and III

In China

2000 participants (less than 70 years)

Ongoing recruitment

Up to 20 years of follow up

Jul. 2019 – Dec. 2049

NCT04010604

- A prospective observational study prior to future clinical trials in SMA type I, II or III, with age at onset less than 17 years, is currently in progress in the United States.

Prospective study over 3 years in SMA type I, II and III

In the United States

120 participants (all ages)

Recruitment completed

3 years of follow up

May 2005 – Dec. 2022

NCT00443066

Cross-sectional study

A retrospective cross-sectional study that was conducted in Brazil among patients with SMA type II or III to characterise their clinical and epidemiological profile, has just ended. The data are currently undergoing analysis.

Retrospective cross-sectional study in SMA type II and III

In Brazil

155 participants (6 months and

Study ended, data undergoing analysis

1 day

May 2020 – Apr. 2021

NCT04404764

Studies of disease manifestations

Several studies are being conducted to better describe upper limb function, and to assess motor functions, motor neuron loss, etc.

- In France, a prospective observational study called ExplorASI, assessing space exploration abilities in children with SMA type I or II, has ended. The data are currently undergoing analysis.

ExplorASI study

In France

30 participants (3 to 16 years)

Study ended, data undergoing analysis

1 visit

Sep. 2017 – Nov. 2019

NCT03223051

▪ An American observational study is in the process of recruiting participants with SMA type III in order to test a portable technology (insoles) to assess gait.

Portable technology to assess gait in SMA type III

In the United States

39 participants (5 years and over)

Ongoing recruitment

1 week of follow up

Nov. 2019 – Aug. 2023

NCT04193085

▪ To follow up motor neuron loss progression among patients with SMA type II or III, a study using the electrophysiological technique, motor unit number estimation (MUNE), is in the process of recruiting patients in America.

Motor unit number estimation in adults with SMA type II or III

In the United States

140 participants (17 to 70 years)

Ongoing recruitment

Up to 15 years of follow up

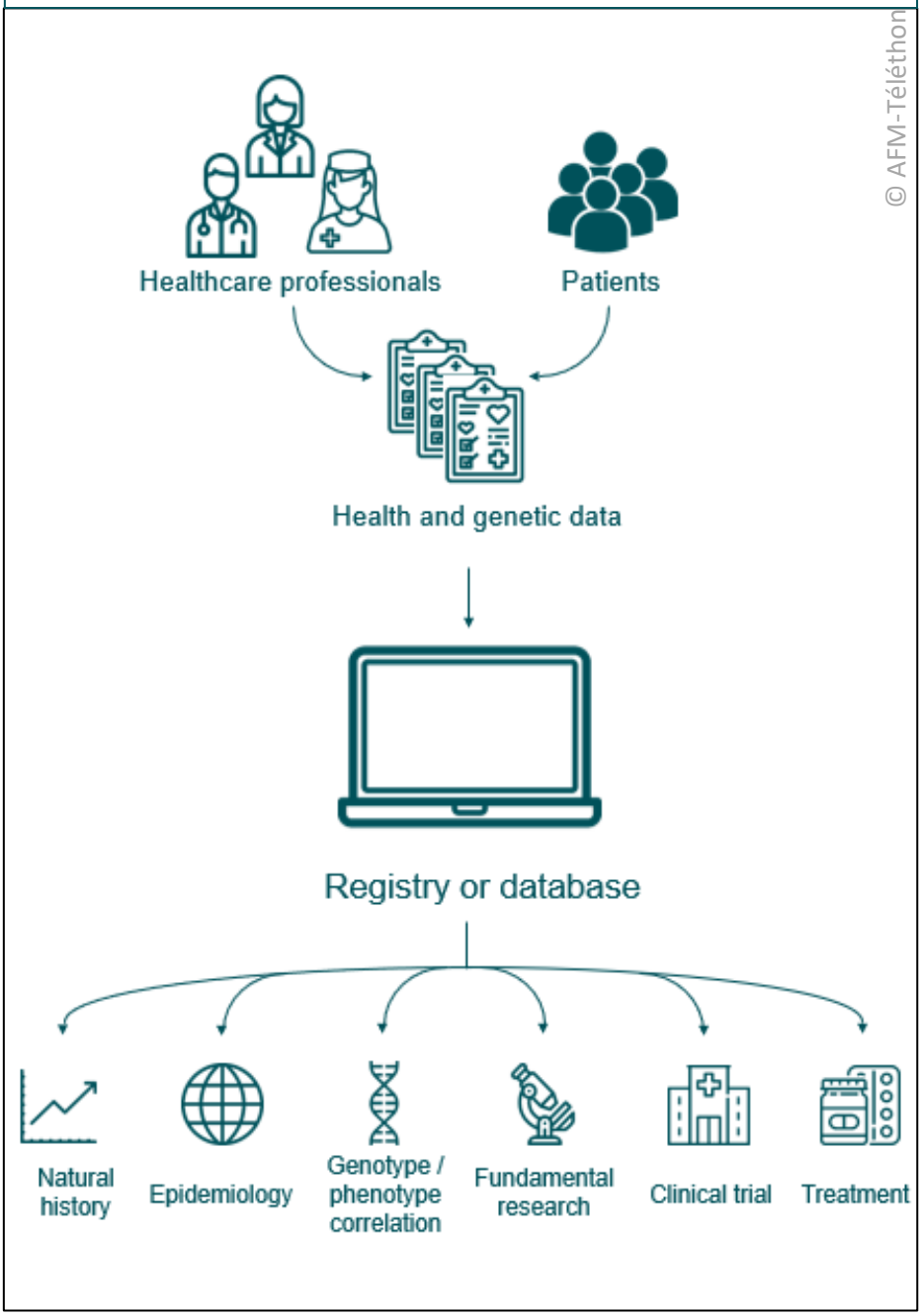
Aug. 2018 – Dec. 2022

NCT04139343

Databases

Databases
Databases consolidate medical and genetic data from patients with the same disease, often without any time limit.
The analysis of collated data helps to clarify the natural history of the disease, to establish genotype/phenotype correlations and to facilitate the recruitment of participants for clinical trials.

Registries and databases
Patient registries and databases are collections of molecular and medical data from patients with a particular disease (with their permission).



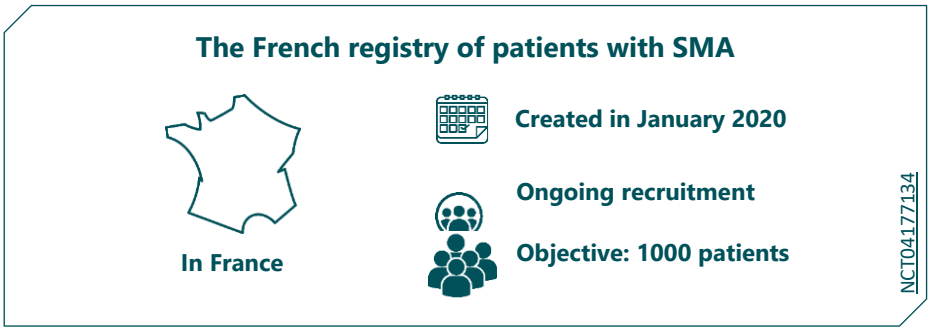
Genotype/phenotype correlation *studies investigate the existence of a relationship between genetic characteristics, the genotype, and characteristics expressing themselves in an observable manner, the phenotype (height, eye colour and shape, hair colour, disease manifestation, etc.).*
This helps to identify whether a relationship exists between the presence of genetic abnormalities and the manifestations of a genetic disease.

The SMA Registry France

The goal of the French registry of patients with SMA is to collect and analyse data from any individual with SMA (of all types, I to IV), whether living or deceased, whether the individual is or has been taking an innovative treatment or not, who has been seen and/or followed up in a reference centre, a centre of expertise or a neuromuscular disease specialised consultation, since September 2016.

- The SMA Registry France, which was set up at the beginning of 2020 and is being led by Prof. Susana Quijano-Roy at the Raymond-Poincaré Hospital in Garches, in conjunction with the clinical research unit at the Ambroise-Paré Hospital (part of the APHP, the Paris Network of Public Hospitals), is intended to last 10 years. Its objective is to collect data from at least 1000 children or adults with SMA.
- In May 2022, 846 patients were included in this registry; 438 children and 408 adults.

Lemoine M et al. Med Sci (Paris). 2021 Nov.



Over time, it should also, in conjunction with similar registries from other sources and/or other countries (Cure-SMA registry, Treat-NMD Universal Registry Platform, SMArtCARE registry, RESTORE registry, etc.) contribute to the optimisation of care for patients, including via innovative therapies.

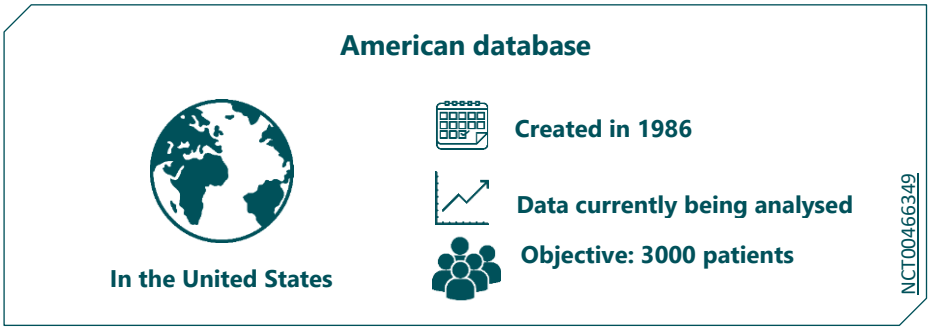
Finkel RS et al. J Neuromuscul Dis. 2020.

*The **Cure SMA** Association is an American not-for-profit Association of parents (of families), whose main mission is to speed up the development of a treatment for SMA. It finances and steers scientific research programmes, finances studies or clinical trials, informs and supports families, etc.*

WEB www.curesma.org/

A database in the United States

The American database, supported by the Cure SMA Association, is one of the largest databases that exists in *SMN1*-related proximal spinal muscular atrophy (SMA).



A database of patients receiving treatment

- Another database, coordinated by AveXis, the firm that developed Zolgensma®, has as its goal the collection of data from patients with SMA, in order to assess the long-term results of different therapeutic options that have recently emerged.

American database of patients receiving treatment

In the United States and in Israel

Created in 2018

Ongoing recruitment

Objective:-500 participants

NCT04174157

A UK registry

The UK SMA patient registry collects the data of patients with SMA in the United Kingdom and Ireland, in order to better describe the disease and identify participants for potential clinical trials.

UK SMA patient registry

In the United Kingdom

Created in July 2008

Ongoing recruitment

Objective:-700 participants

NCT04292574

The *SMArtCARE German Observational Study*

SMArtCARE is an observational study of German-speaking patients with *SMN1*-related proximal spinal muscular atrophy, residing in Germany, Austria or Switzerland. The objective is to learn more about the progression of the disease and its daily impact.

▪ This database, which was constructed to take into account data in a real-life setting regarding both the impact of nusinersen (or other upcoming innovative therapies) and aspects of traditional care, aims to be a prospective longitudinal follow-up tool, aimed at doctors themselves (whether or not they are prescribers), researchers, payers and patient associations. Healthcare companies are linked to the setting up of SMArtCARE, but not with the analysis of its data.
Pechmann A et al. Orphanet J Rare Dis. 2019 Jan.

***SMArtCARE* database**

Abroad (outside France)

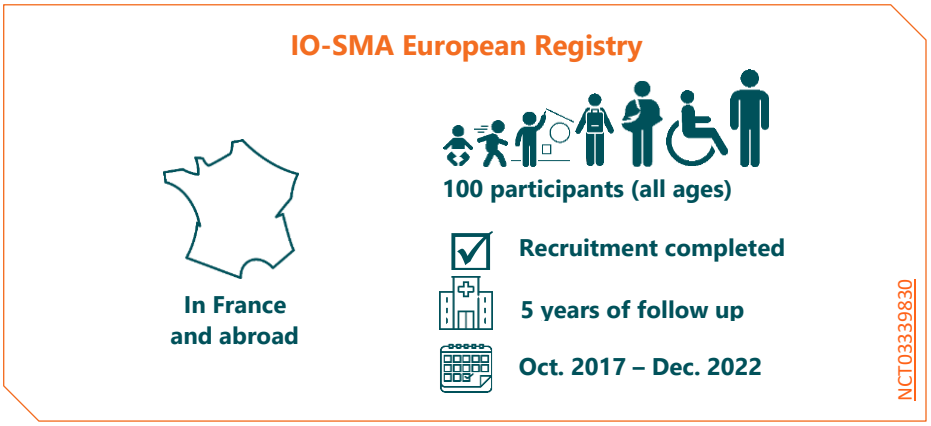
Created in August 2018

Ongoing recruitment

WEB https://www.smartcare.de/en/index.html

European registry of patients with SMA

A European registry is in the process of recruiting, in order to describe the progression, over a 5-year period, of SMA type I, II and III with age of onset under 18 months, with or without treatment.



Neonatal screening

The neonatal screening of a disease consists of systematically testing for the disease at birth, in all newborns.

In France, screening of this type has been established for six diseases to date: phenylketonuria (since 1972), congenital hypothyroidism (1978), congenital adrenal hyperplasia (1995), sickle-cell disease (1989 in the French overseas territories and 1995 in mainland France), cystic fibrosis (2002) and, more recently, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (2020).

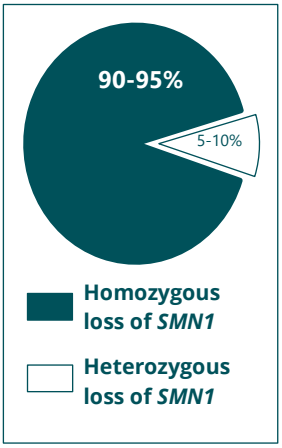
The third Rare Diseases French National Plan, which covers the period 2018-2022, plans to increase the number of diseases screened for, and to speed up the implementation of new neonatal screening programmes.

Access to treatment as early as possible

In SMA, this topic has become central since the recent marketing authorisation of the three disease-modifying treatments, Spinraza®, Zolgensma® and Evrysdi®, which have shown a better efficacy (in particular faster and more significant motor improvement) if they are initiated before disease symptoms manifest (pre-symptomatically) rather than afterwards (symptomatic phase). This shows the importance of initiating these treatments as early as possible, which supposes an early diagnosis of the disease. Neonatal screening makes this possible.

How is the molecular diagnosis of SMA performed?

In 90 to 95% of cases, *SMN1*-related proximal spinal muscular atrophy (SMA) is caused by a complete loss of the *SMN1* gene (heterozygous loss with no copies of the *SMN1* gene). Using a blood draw, the most commonly used diagnostic technique in SMA will identify if there are no copies of the *SMN1* gene. Other techniques will determine genetic abnormalities in the *SMN1* gene or the number of copies of the *SMN2* gene.



▪ A published article about two neonatal cases of SMA in the United States suggests that the early initiation of a treatment in infants is crucial for treatment response and motor development.

The first child, diagnosed at 5 days old (with zero copies of *SMN1*, 2 copies of *SMN2*), asymptomatic at 23 days, was able to start a treatment with Zolgensma® at 24 days. The child was able to walk at 11 months, and at 1 year, the child's motor development was normal.

The second child, diagnosed at 5 days old (with zero copies of *SMN1*, 2 copies of *SMN2*), started to show signs of motor and respiratory involvement at 19 days. A treatment was initiated with Spinraza® at 20 days (4 injections in total), then with Zolgensma® at 4 months. At 1 year old, although presenting clinical improvement, the child still showed significant motor development delay and difficulty swallowing.

Butterfield RJ et al. Semin Pediatr Neurol. 2021 Jul.

The DEPISMA project in France

DEPISMA project
Initiated by AFM-Téléthon, the FILNEMUS network, Strasbourg University Hospital and Bordeaux University Hospital, a forerunner pilot project lasting two years, the goal of which is to demonstrate the feasibility of SMA neonatal screening in two French regions, Grand Est and New Aquitaine, obtained ethics committee authorisation in May 2022 and is due to start sometime this year. The objective subsequent to this is national deployment.

The genetic test will be performed by collecting a drop of blood on plotting paper, to test for the absence of both copies of the *SMN1* gene. If the infant tests "positive", a confirmation of the SMA diagnosis will be performed, and the infant will receive care at one of the FILNEMUS network Neuromuscular Disease Reference Centres, in order to have access to one of the authorised treatments.

Experiences of neonatal screening worldwide

Several countries have already deployed pilot programmes for the neonatal screening (i.e. screening at birth) of SMA, for example Germany, Belgium, Australia, Taiwan, etc. In the United States, neonatal screening of SMA was added in 2018 to the recommended screening panel (RUSP for recommended uniform screening panel). Thus, in June 2022, a total of 44 states in the USA perform this screening, which corresponds to 95% of US newborns.

Did you know?

A European Alliance for the neonatal screening of SMA
This Alliance, which AFM-Téléthon belongs to, was launched on 31 August 2020 by SMA Europe in order to advocate neonatal screening of this condition in Europe. It is asking that, by 2025, the neonatal screening programmes for all European countries include a systematic test for SMA. The members of the Alliance will draft a white book on this neonatal screening, which will gather together scientific evidence and studies justifying the inclusion of SMA in these national neonatal screening programmes.
SMA Newborn Screening Alliance

SMA Europe *is an organisation encompassing 20 associations representing patients with spinal muscular atrophy in Europe, including AFM-Téléthon. Its goal is to improve the care and quality of life of patients, to speed up research, and to favour access to treatments.*
WEB www.sma-europe.eu/

Results in the last few months

The establishment of genetic screening programmes for SMA at birth is continuing worldwide, with new results published.

- In Canada, in the province of Ontario, SMA was included in its neonatal diagnostic programme, initially as a pilot study from January 2020, then permanently in July 2020. Of 139,800 infants screened, 5 were diagnosed with SMA and were referred to a centre of expertise, at a median age of 9 days. Three of these were treated, at a median age of 24 days, even though they were still asymptomatic.
Kernohan KD et al. Can J Neurol Sci. 2021 Oct.

- In Belgium, a pilot neonatal screening programme entitled "Sun May Rise on SMA" was conducted between March 2018 and February 2021. It was initially restricted to the Liège region, then was very quickly extended to the whole of south Belgium.
Of the 136,339 newborns tested, this programme allowed 9 of them to be diagnosed with SMA. A tenth infant was, however, identified outside the

screening process, after initial symptoms appeared. As such, these 10 babies were able to receive a treatment.
This SMA neonatal screening programme has now become official in the south of Belgium, and this should also become the case in 2022 in the north of the country.
Boemer F et al. Sci Rep. 2021 Oct.

▪ The American Association, Cure SMA, has also established a registry for the neonatal screening of SMA in the United States, in order to improve care and develop new treatments.
WEB www.curesma-enrollment.rexdb.net/caregiver

Other clinical/scientific advances

New therapeutic avenues

▪ Several scientific studies have helped to advance the hypothesis that preserving or activating **certain molecules in the neuromuscular junction** might constitute an additional therapeutic target in the treatment of SMA.
Feng Z et al. Int J Mol Sci. 2021 Jul.

▪ A Chinese study has analysed, in the cells derived from patients with SMA and in mouse models of the disease, the effects of administering **two antisense oligonucleotides targeting the key *SMN2* methylation sites**.
A significant increase in the production of SMN protein was observed in the cell lines after the oligonucleotides were added. The authors obtained similar results in the SMA cells treated with nusinersen (Spinraza®), another antisense oligonucleotide that acts, this time, on *SMN2* splicing.
The intrathecal administration of one of the two antisense oligonucleotides (ASO-P1) in mice increased the levels of SMN protein in different organs (muscles, brain, spinal cord, liver) and increased their life expectancy. In this study, a treatment combination of nusinersen and ASO-P1 increased the level of functional SMN in the cells to a greater extent than either ASO-P1 or nusinersen alone.
Wang J et al. Hum Mol Genet. 2021 Dec.

▪ Several studies have investigated the influence of certain molecules or certain environmental factors on the peripheral motor neurons, and these could be future therapeutic targets in SMA. Among these, modulation of the **GATA6 protein or intermittent treatment at high temperature** have demonstrated, in vitro, their beneficial effect on motor neuron function.
Allison RL et al. Glia. 2022 May.
Dominguez CE et al. Hum Genet. 2022 Feb.

Biological markers

A biological marker, also referred to as a biomarker, is a measurable characteristic that reflects a normal or pathological biological process. The identification of new biological markers for a disease is very important in following up its progression and/or the efficacy of new treatments, whether these markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).

▪ Several studies are currently being conducted to attempt to measure the impact of a treatment in terms of laboratory readings, and to assess its possible correlation with the patient's motor function. In particular, the study of motor neurone-related RNA products in the cerebrospinal fluid (CSF) of patients, of microRNAs and of neurofilaments could prove promising.

Did you know?

Neurofilaments

Neurofilaments (NFs) are the primary structural proteins in neurons. The detection of high concentrations of NFs in the blood or the cerebrospinal fluid indicates neuronal lesions, regardless of the cause. Newborns with *SMN1*-related proximal spinal muscular atrophy (SMA) thus present particularly high levels of circulating NFs, of up to 45 to 50 times the concentration observed in individuals not affected by SMA.

▪ An American study has examined **serum neurofilament levels** in 90 children less than 3 years of age, with SMA, treated or not treated with nusinersen (Spinraza®) and/or onasemnogene abeparvovec (Zolgensma®), compared to 13 children without SMA.
According to its results, the increase in levels of NFs in the blood, during the first months of life, is inversely proportional to the number of copies of *SMN2* and to the compound muscle action potential (CMAP), which helps to monitor motor neuron involvement.
Alves CRR et al.Mol Ther Methods Clin Dev. 2021 Oct. *Welby E et al. Hum Mol Genet. 2021 Dec.* *Nitz E et al. Ann Clin Transl Neurol. 2021 Oct.* *Pino MG et al . Biomark Insights. 2021 Aug.*

▪ Italian researchers have studied the expression of microRNA in the muscle and blood samples of patients with SMA or patients without the disease. More than 100 microRNA show modified expression, and of these, 3 microRNA, **miR-181a-5p, miR-324-5p and miR-451a**, show significantly increased expression in the samples of patients with SMA.
Abiusi E et al. Elife. 2021 Sep.

▪ Studying blood draws of infants with SMA type I, aged under one year, and compared to those of infants without the disease, an American team identified the **HSP70 protein** as a biological marker that could be useful in monitoring the progression of SMA over the first year of life.
Eichelberger EJ et al. Ann Clin Transl Neurol. 2021 Jul.

Tools for monitoring disease progression

Motor function measure (or MFM) is a scale developed by a team from Lyon that has gradually made its mark internationally. Made up of 32 items rated 0 to 3 (MFM32), this scale investigates three dimensions: D1 for standing position and transfers, D2 for axial and proximal motor function, and D3 for distal motor function.

▪ An international consortium made up of clinicians, patient association representatives and members of Roche, has conducted a study to assess the patient point of view with regard to the relevance and significance of **MFM**. By analysing the clinical course of patients and its impact on them and their caregivers, it shows that the change in score with respect to MFM must be equal to or greater than 3 points to be felt significantly.
Duong T et al. Front Neurol. 2022 Jan.

▪ A study conducted on several groups of adolescents and adults with SMA has shown certain **clinical/functional criteria** (such as SMA functional rating scale, MoviPlate, pinch strength, etc.) to be tools that may help to assess disease severity.
Gavriilaki M et al. Neuromuscul Disord. 2022 Mar.

▪ Fatigue is a symptom that is very difficult to assess in clinical practice, since it is multifactorial in origin, and yet it is the core functional complaint of patients with SMA. It is therefore crucial to monitor in therapeutic trials. Certain scales such as the **Multidimensional Fatigue Inventory** seem to be reliable tools to assess it.
Binz C et al. Ann Clin Transl Neurol. 2022 Mar.

▪ German researchers have studied the feasibility and cost-effectiveness, in 10 children with SMA type I and II, aged between 2 and 46 months, of a **tool to analyse movement**. This technique has the advantage that it can

study mobility in three dimensions of space, but without having to place sensors on the child's body. It seems to provide a good correlation with CHOP-INTEND score, which has been validated and is conventionally used in studies.
Blaschek A et al. J Neuromuscul Dis. 2022.

▪ **Multispectral opto-acoustic tomography (MSOT)** is a non-invasive technique requiring a probe that is moved across different muscle tissues. Assessed in 10 patients with SMA and 10 patients without the disease, it helped, in particular, to quantify the degree of muscular atrophy and to establish correlations between this measurement and other functional scores used in SMA, among subjects who were treated or not treated.
Regensburger AP et al. 2021 Nov.

Wirelessly connected wristbands in neuromuscular diseases

▪ A British study has shown that the **Fitbit® wirelessly connected watches** are practical and useful in assessing the physical exercise performed by patients on a daily basis. Participants said, for example, that they were more attentive to their daily activity, and that it was easy to follow the data.
However, these wirelessly connected objects remain less precise than medical devices, in particular in measuring heart rate or number of steps.
Sarah F Roberts-Lewis et al. Disabil Rehabil . 2021 Oct

Wheelchair hockey, a sport that is beneficial in SMA and DMD

Playing wheelchair hockey improves quality of life and well-being, according to an Italian study conducted in male subjects, for two neuromuscular diseases. The study included 11 men with Duchenne Muscular Dystrophy (DMD) and 14 men with *SMN1* gene-related proximal spinal muscular atrophy (SMA), aged between 18 and 40 years. 15 of them played wheelchair hockey, and the others did not do any sport.
The comparison of the two groups showed that playing this adaptive sport significantly improved the **quality of life score**, by 4.4 points.
Carraro E et al. PM R. 2021 Nov

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* *

▪ Throughout the year, follow neuromuscular disease research news on:
WEB www.afm-telethon.fr/en