Taylor & Francis
Taylor & Francis Group

Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: www.tandfonline.com/journals/iern20

A plain language summary of the SAPPHIRE clinical trial of apitegromab in children and young adults with spinal muscular atrophy

Thomas O. Crawford, Laurent Servais, Eugenio Mercuri, Heike Kölbel, Nancy Kuntz, Richard S. Finkel, Jena Krueger, Kaitlin Batley, Sally Dunaway Young, Jing L. Marantz, Guochen Song, Bert Yao, Guolin Zhao, Jose Rossello, Giridhar S. Tirucherai, Elena Stacy Mazzone, Russell J. Butterfield, Marta Gomez Garcia de la Banda, Andreea M. Seferian, Valeria A. Sansone, Liesbeth De Waele, W. Ludo van der Pol, Claude Cances, Astrid Pechmann, Basil T. Darras & for the SAPPHIRE Study Group

To cite this article: Thomas O. Crawford, Laurent Servais, Eugenio Mercuri, Heike Kölbel, Nancy Kuntz, Richard S. Finkel, Jena Krueger, Kaitlin Batley, Sally Dunaway Young, Jing L. Marantz, Guochen Song, Bert Yao, Guolin Zhao, Jose Rossello, Giridhar S. Tirucherai, Elena Stacy Mazzone, Russell J. Butterfield, Marta Gomez Garcia de la Banda, Andreea M. Seferian, Valeria A. Sansone, Liesbeth De Waele, W. Ludo van der Pol, Claude Cances, Astrid Pechmann, Basil T. Darras & for the SAPPHIRE Study Group (2026) A plain language summary of the SAPPHIRE clinical trial of apitegromab in children and young adults with spinal muscular atrophy, Expert Review of Neurotherapeutics, 26:1, 101-120, DOI: 10.1080/14737175.2025.2579903

To link to this article: https://doi.org/10.1080/14737175.2025.2579903

EXPERT REVIEW OF NEUROTHERAEUTICS
2026, VOL. 26, NO. 1, 101–120
https://doi.org/10.1080/14737175.2025.2579903

Plain Language Summary of Publication

EXPERT REVIEW
OF NEUROTHERAPEUTICS

A plain language summary of the SAPPHIRE clinical trial of apitegromab in children and young adults with spinal muscular atrophy

Thomas O. Crawford[a], Laurent Servais[b], Eugenio Mercuri[c], Heike Kölbel[d], Nancy Kuntz[e], Richard S. Finkel[f], Jena Krueger[g], Kaitlin Batley[h], Sally Dunaway Young[i], Jing L. Marantz[j], Guochen Song[j], Bert Yao[j], Guolin Zhao[j], Jose Rossello[j], Giridhar S. Tirucherai[j], Elena Stacy Mazzone[k], Russell J. Butterfield[l], Marta Gomez Garcia de la Banda[m], Andreea M. Seferian[m], Valeria A. Sansone[n], Liesbeth De Waele[o], W. Ludo van der Pol[p], Claude Cances[q], Astrid Pechmann[r], Basil T. Darras[s], for the SAPPHIRE Study Group*

Author affiliations can be found at the end of the article

First draft submitted: 5 September 2025; Accepted for publication: 21 October 2025

Where can I find the original article on which this summary is based?

The original article title is 'Efficacy and safety of apitegromab in nonambulatory type 2 or 3 spinal muscular atrophy (SAPPHIRE): a phase 3, double-blind, randomized, placebo-controlled trial.' It can be found at: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(25)00225-X/abstract. The article cannot be accessed for free.

Summary

What was the trial about?

Spinal muscular atrophy (SMA) is a rare and serious progressive, worsening genetic disease. Children and adults living with SMA have low levels of a **protein** called the **survival motor neuron (SMN) protein**. Without enough of this protein, the nerve cells that control muscles (**motor neurons**) begin to die. As a result, the muscles become smaller (a condition called **muscle atrophy**) and weaker. Over time, this leads to a loss of normal movement (called **motor function**) and muscle control.

Treatments that increase SMN protein levels (SMN-targeted treatments) improve motor neuron survival and thus overall motor function. However, many individuals living with SMA who are taking these treatments still experience reduced motor function compared with people without SMA.

How to say (download PDF and double click sound icon to play sound)...

- **Atrophy:** AT-ruh-fee
- **Apitegromab:** a-PIT-eh-gro-mab
- **Evrysdi (risdiplam):** ev-RIZ-dee; RIZ-di-plam
- **Monoclonal antibody:** mon-oh-CLON-al AN-ti-bod-dee
- **Myostatin:** my-oh-STAT-in
- **Nonambulatory:** non-AM-byu-la-tor-ee
- **Neuromuscular:** nyur-oh-MUSS-kyu-ler
- **Placebo:** pluh-SEE-boh
- **Spinal muscular atrophy:** SPY-nuhl MUSS-kyu-ler AT-ruh-fee
- **Spinraza (nusinersen):** spin-RAH-za; noo-sin-UR-sin
- **Zolgensma (onasemnogene abeparvovec-xioi):** zol-GEN-zma; on-a-SEM-no-gene ab-eh-PAR-vo-vec x i o i

Taylor & Francis
Taylor & Francis Group

A new potential treatment called **apitegromab** directly targets **myostatin** in muscles to improve motor function. This summary describes the SAPPHIRE clinical trial. In this study, patients with SMA who were already receiving treatments that target the SMN protein (SMN-targeted treatments), also received apitegromab.

What was the objective?
The aim of the SAPPHIRE trial was to see how well apitegromab worked and what side effects it might cause over one year. The study compared apitegromab to a **placebo** treatment in patients with SMA who were already receiving SMN-targeted treatments.

What were the results?
After 1 year of continued treatment, motor function improved in patients treated with apitegromab compared with those who received placebo. Improvements with apitegromab were seen across different age groups and different dose levels. Patients tolerated apitegromab well, meaning that side effects were similar between patients receiving apitegromab or placebo and side effects caused by apitegromab were minimal. Most of the side effects were either common among people living with SMA or likely caused by the SMN-targeted treatments the patients were already receiving.

What do the results mean?
These results suggest that directly targeting muscles with apitegromab has the potential to improve motor function for people living with SMA who are already receiving SMN-targeted treatments.

Key takeaways:

- The SAPPHIRE clinical trial showed that treatment with apitegromab led to improvements in motor function for patients with SMA who were also receiving SMN-targeted treatment
- Motor function improvements were notable in patients who received apitegromab, regardless of age, apitegromab dose, type of SMN-targeted treatment, or duration of SMN-targeted treatment
- Apitegromab treatment led to minimal side effects
- Combining SMN-targeted treatments with muscle-targeted treatments like apitegromab may help improve or maintain motor function for patients with SMA

Spinal muscular atrophy: A rare disorder that affects the nerves controlling muscles, causing weakness and difficulty with movement. This occurs when the body does not make enough of the survival motor neuron (SMN) protein, which is essential for muscle strength and control.
Proteins: Molecules made from genes that carry out specific, essential functions in cells and tissues.
Survival motor neuron (SMN) protein: A vital protein that helps keep the nerve cells that control muscles healthy and working properly.
Motor neuron: A nerve cell that controls muscles by sending signals from the brain or spinal cord to the muscles.
Muscle wasting (atrophy): Loss or shrinking of muscles that makes them smaller and weaker.
Motor function: The ability to control and coordinate muscle contractions and body movements, such as sitting up, crawling, walking, and picking up or grabbing items.
Apitegromab: A new muscle-targeted treatment for SMA being investigated in clinical trials. It works by preventing the conversion of immature myostatin into its mature, or active, form. This releases the myostatin 'brake' on muscle growth, leading to increased muscle mass and strength.
Myostatin: A protein in muscle cells that regulates muscle growth. Pro-myostatin and latent myostatin are 'immature', or inactive forms of myostatin that do not have any effect on muscle. Immature myostatin gets converted to mature myostatin, an active form of myostatin that acts as a 'brake' on muscle cells to restrict muscle growth.
Placebo: An inactive substance that looks the same and is given the same way as an active drug or treatment being tested in a clinical trial.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. Apitegromab is an investigational treatment not yet approved by any regulatory agencies, such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), to treat the condition under study that is discussed in this summary.

Who is this article for?

This article is intended for patients living with SMA, their families, and caregivers. It explains what apitegromab is and shares the results of the SAPPHIRE clinical trial. It may also be helpful for patient societies, patient advocates, and healthcare professionals, including those helping patients find the best care for their SMA.

Who sponsored this study?

Scholar Rock, Inc. **sponsored** the SAPPHIRE trial.

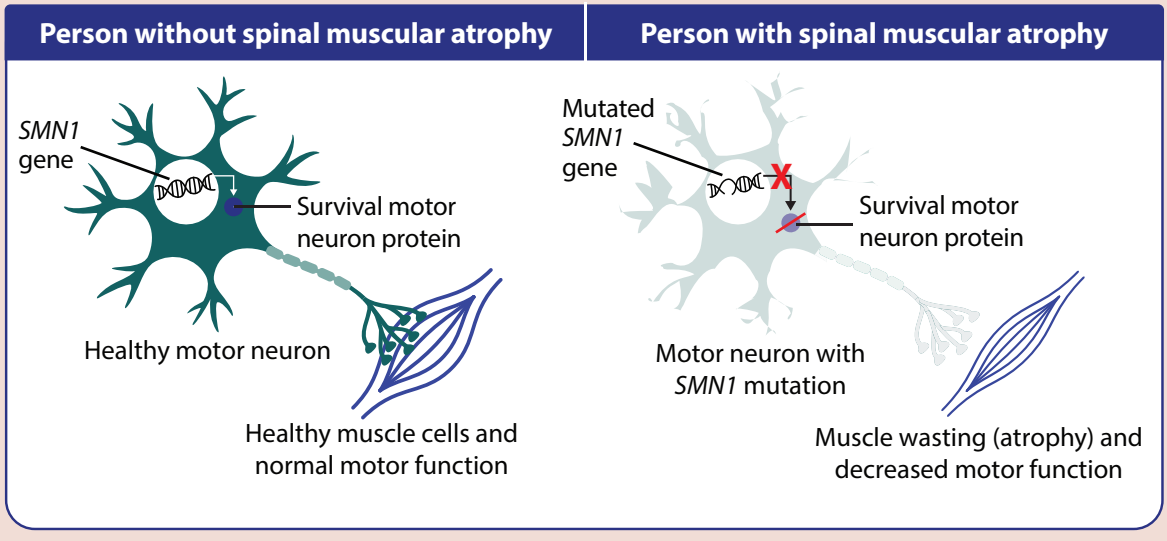
Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is SMA?

Spinal muscular atrophy (SMA) is a rare genetic disorder in which **mutations** in the **gene** called *SMN1* prevent the body from producing enough of a protein called survival motor neuron (SMN). A second gene, *SMN2*, also produces SMN protein; however, unlike *SMN1*, which produces fully functional SMN protein, only a small amount of the SMN protein produced by *SMN2* functions fully.

Mutation: A change in the DNA of a gene that can affect how the protein made by the gene functions.
Gene: A segment of DNA that carries instructions for making specific proteins.
Skeletal muscle: The type of muscle that is connected to bones and controls movement.
Wasting (atrophy): Decrease in size or wasting away of a body part or organ.

SMN protein is essential for the function and survival of neurons in the spinal cord (known as motor neurons) that carry messages from the brain to **skeletal muscles** throughout the body, enabling coordinated muscle movements. Without enough SMN protein, motor neurons malfunction and die, and the muscles they control cannot function properly. This results in **wasting (atrophy)** and weakness that worsen over time in muscles that are responsible for activities such as sitting, crawling, walking, breathing, and swallowing.



The severity of SMA depends on how many *SMN2* gene copies a person has. More copies usually mean the body can make more SMN protein.

Traditionally, SMA has been classified into five types (0 through 4) based on symptom severity and the age when symptoms start.

- People with fewer *SMN2* copies (**type 0 or 1**) have symptoms that begin before birth or during infancy, fail to achieve age-appropriate motor milestones (may never be able to roll over or sit on their own), and have drastically reduced life expectancy.
- People with more *SMN2* copies (**type 2 or 3**) may experience symptoms such as limited ability or inability to stand or walk that appear later in childhood. They often have secondary complications, such as pneumonias, severe scoliosis and limb contractures. Life expectancy may be full, but often many medical therapies are necessary for a lifetime.
- The mildest form of SMA (**type 4**), typically manifests as mild weakness or fatigue and begins later in teen years to young adulthood.

SMA type	Typical age range when symptoms appear	Maximum motor skill achieved with supportive care	Survival with supportive care (Survival without major complications, meaning a patient did not need a ventilator for more than 16 hours a day over a period of at least 14 days)
0	Fetal	—	Days to weeks
1	1–6 months	Head control, no sitting or rolling	Months (around 10 months, on average)
2	7–18 months	Sits, no walking	Years (over 20 years, on average)
3	1.5–10 years	Walks (limited)	Normal
4	Greater than 18 years	Walks (normal)	Normal

Type 0 or 1 SMA: SMA that develops before birth (type 0) or early after birth (type 1). Type 0 is the most severe form of SMA; type 1 is less severe in comparison.
Type 2 or 3 SMA: SMA that develops after 6 months of age (type 2) or 18 months of age (type 3) and is considered less severe than type 1 SMA.
Type 4 SMA: SMA that develops later in life (late teenage years to early adulthood) and is the least severe type compared to types 0-3.

What are the currently available treatments for SMA?

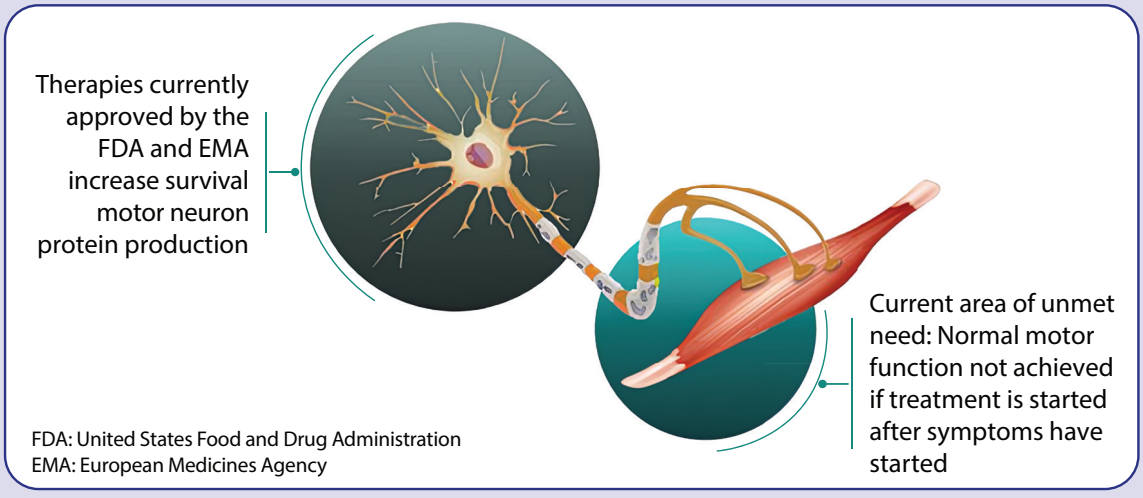
There are three approved treatments for SMA, all of which are 'SMN-targeted,' meaning they work to increase the amount of SMN protein produced by the body. Treatments approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are:

- Nusinersen (Spinraza) for children and adults
- Onasemnogene abeparvovec-xioi (Zolgensma) for children under 2 years old, and
- Risdiplam (Evrysdi) for children, including newborns, and adults

The success of these treatments often relates to the age a patient starts treatment and the amount of damage done by the lack of SMN protein prior to starting treatment. If given early in life, these treatments greatly improve the health outlook; given later in life, the benefit is less, though they slow worsening of disease progression and increase survival. In addition to this, SMN-targeted treatments also help patients with SMA reach movement goals that were once thought to be impossible.

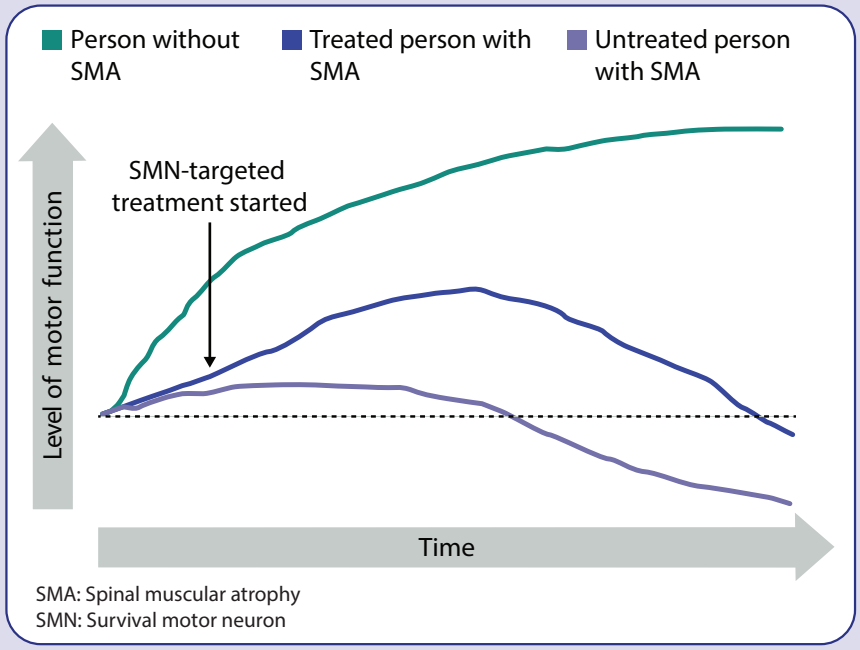
What are the limitations of current SMA treatments?

Once motor neurons are lost, they cannot grow back. Current treatments for SMA can slow or stop further loss, but they cannot bring back motor neurons that were already lost. As a result, muscles with reduced motor neuron connections are weakened, and motor function is compromised.



While people using these treatments do see significant improvements in motor function, many may not achieve levels of function normal for people without SMA. Because SMA gets worse over time, the improvement possible from treatment diminishes the longer treatment is delayed.

With SMN-targeted treatments, some, but not all, of that loss can be recovered. In some cases, however, the improvements from treatment in the first 2 to 4 years may be reduced and muscle function can slowly return to where it was before treatment began. This can happen about 5 years after starting treatment. In those patients, there is a need for new treatments that directly target muscles, improve motor function, and prevent any further losses in motor function.

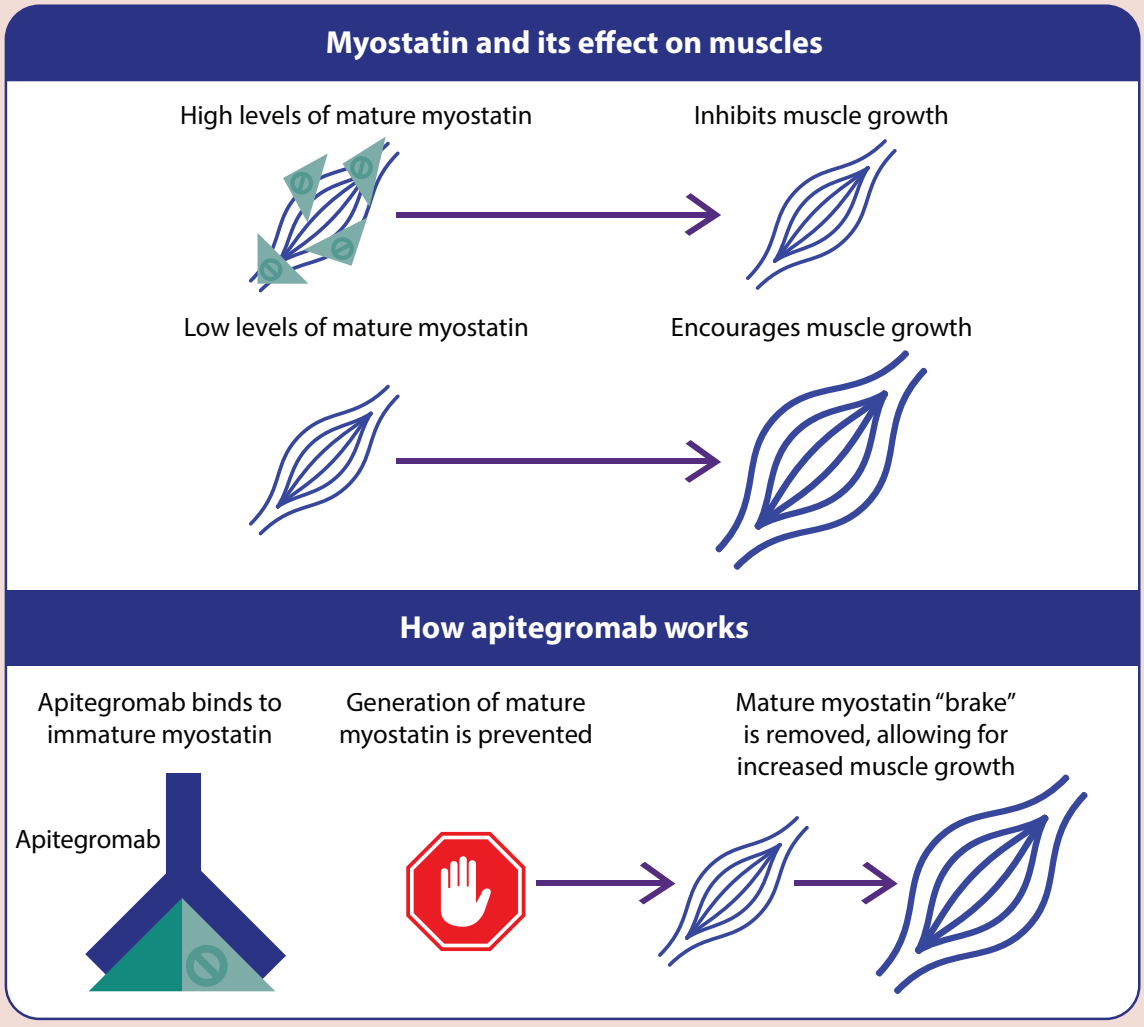


What is apitegromab, and how does it work for SMA?

Unlike current SMA treatments that target SMN protein levels in motor neurons, apitegromab is a muscle-targeted treatment that has the potential to improve muscle size and strength.

Apitegromab is a **monoclonal antibody** therapy that **selectively** attaches to early forms of myostatin, when it is not yet an active signaling hormone. Myostatin is a natural substance made by muscle cells that helps control how much muscle you build, but its activity is backwards from what might be expected. High levels of myostatin slows down muscle growth, and low levels encourage muscle growth. By binding myostatin before it becomes active, apitegromab decreases the amount of myostatin found in muscles, which then takes the 'brake' off muscle growth. In animal models, apitegromab has been shown to help increase muscle size and strength.

Monoclonal antibody: A type of protein that is made in a laboratory and is designed to bind to specific target proteins in the body. These man-made proteins mimic the action of the natural antibodies produced by our immune system but are engineered to treat certain diseases more precisely than natural antibodies.
Selectivity: The ability to interact with a specific, intended target with very limited or no interaction with other targets.



Taylor & Francis
Taylor & Francis Group

What was the purpose of the SAPPHIRE trial?

SAPPHIRE was designed to evaluate the safety and **efficacy** of apitegromab in people living with SMA. The **phase 3** SAPPHIRE trial provides evidence that regulatory agencies can review when considering approving apitegromab use in medical practice.

- SAPPHIRE researchers evaluated whether apitegromab could improve motor function in patients who were also receiving an SMN-targeted treatment (either nusinersen or risdiplam)
- Two different doses of apitegromab were studied

Efficacy: A description of how well a treatment works in the controlled conditions of a clinical trial. Efficacy differs from effectiveness, as effectiveness describes how well a treatment works in real-world conditions (e.g. fewer controls, larger and broader patient population).
Phase 2 trial: A clinical trial that evaluates the efficacy of a new treatment for a specific disease and gathers information about its safety.
Phase 3 trial: A clinical trial that typically includes more patients than a **phase 2 trial** and compares a new treatment with a standard treatment to see how well the new treatment works and how safe it is.

The main questions the researchers wanted to answer were:

- Does apitegromab improve motor function compared with placebo in people living with SMA and receiving an SMN-targeted treatment?
  - » In clinical trials, researchers oftentimes use a placebo treatment, which is a harmless treatment with no active medicine, to compare against the real 'active' treatment to see if it really works
- When given at the doses studied, is apitegromab safe for people living with SMA?

How was the trial carried out?

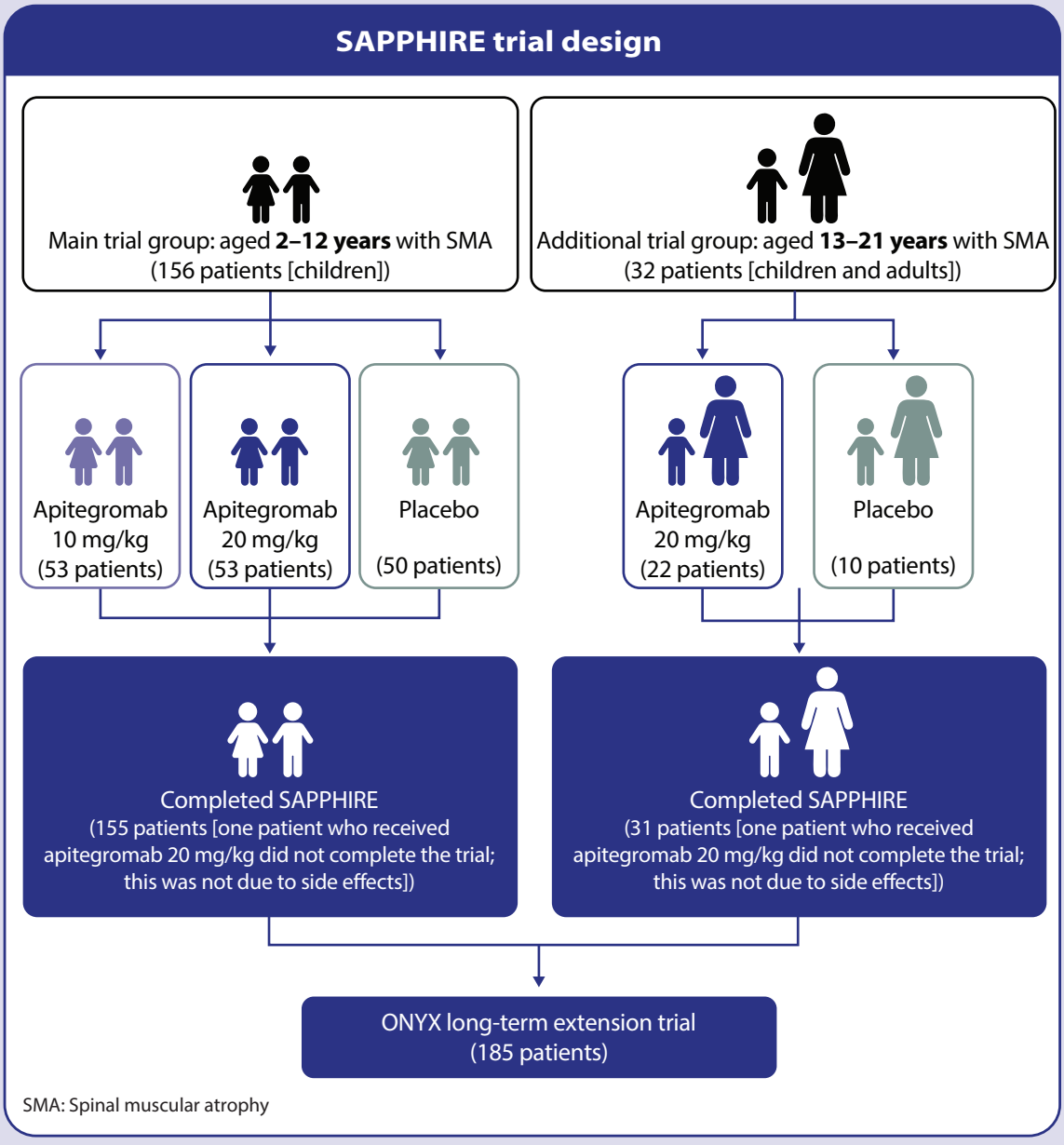
SAPPHIRE was an advanced level clinical trial, 'phase 3', that was designed to evaluate the safety and efficacy of apitegromab in patients with SMA who were already receiving an SMN-targeted treatment (nusinersen or risdiplam).

The main trial group included 156 patients aged 2–12 years. They were **randomized** to receive either apitegromab at 10 milligrams per kilogram of body weight (mg/kg), apitegromab at 20 mg/kg, or placebo, the non-active treatment, by **intravenous (IV) infusion** every 4 weeks for 1 year.

The trial also included an additional group of 32 patients aged 13–21 years who were randomized to receive either apitegromab at 20 mg/kg or placebo.

As a phase 3 clinical trial, patients and investigators were 'blinded'. This is the best way to prove safety and efficacy, as neither the patients nor the researchers knew whether a patient received apitegromab or placebo.

Randomization: The process of assigning patients in a clinical trial to different study groups by chance, rather than by choice. Randomization helps ensure that treatment groups are as similar as possible to increase the likelihood that differences between groups are due to their treatment (e.g. apitegromab versus placebo) and not to any other factor.
Intravenous (IV) infusion: A method to deliver medicine or fluids directly into a person's bloodstream.



After completing the SAPPHIRE trial, all but one participant chose to continue apitegromab treatment in the ONYX clinical trial. ONYX is an **open-label**, long-term extension trial in which all patients receive apitegromab to evaluate its impact over a longer treatment period than was studied in SAPPHIRE.

Open-label trial: Type of clinical trial in which both the researchers and patients know what treatment the patients are receiving.

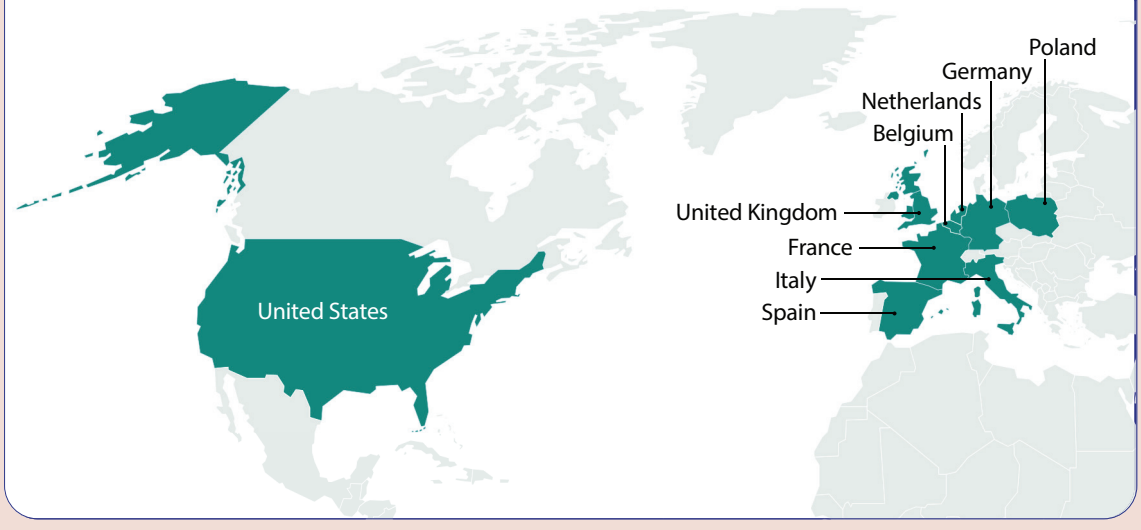
Who took part in the trial?

SAPPHIRE was conducted at 48 research sites in nine countries across Europe and North America. The trial enrolled patients aged 2–21 years with SMA type 2 or 3 receiving either nusinersen or risdiplam who were unable to walk independently (**nonambulatory**).

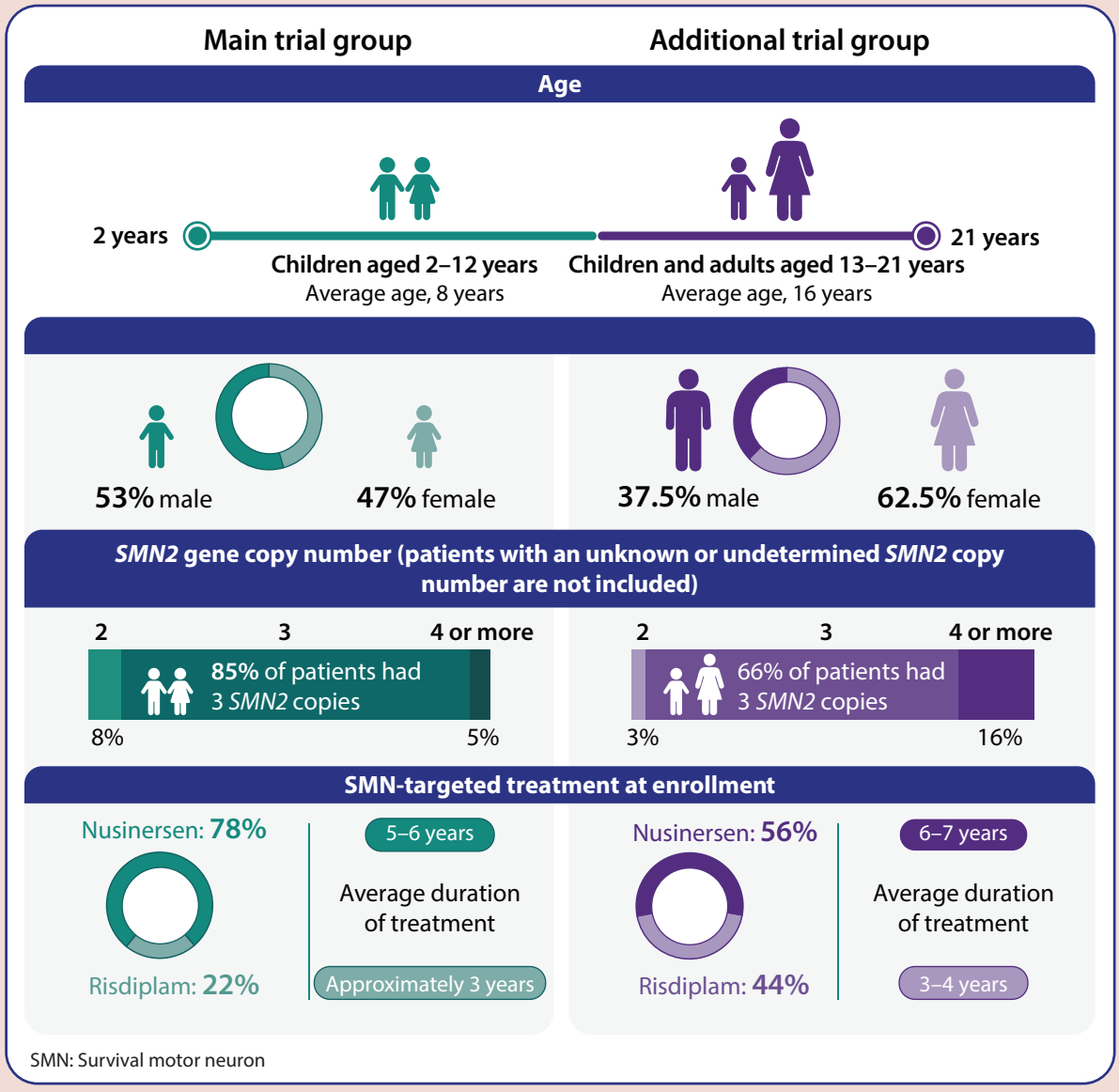
Individuals with a history of severe hypersensitivity reactions to nusinersen or risdiplam, or who had severe scoliosis or contractures, were not **eligible** to participate in SAPPHIRE.

Nonambulatory: Unable to walk independently
Eligible: Meeting the set of requirements necessary to take part in a clinical trial. If an individual does not meet the requirements, they are not eligible to participate in the trial.

Global study locations



Characteristics of patients in the SAPPHIRE study



SMN: Survival motor neuron

The main trial group, consisting of patients aged 2–12 years, was the primary focus of the study. An additional trial group of patients aged 13–21 years was also included to further explore the effects of apitegromab in an older patient population.

What was evaluated in the trial?

SAPPHIRE evaluated whether apitegromab could improve motor function after 1 year of treatment. Motor function was assessed using three measures:

Main assessment

Hammersmith Functional Motor Scale-Expanded (HFMSE)

- Scoring system designed to evaluate motor function in people with SMA type 2 or 3
- Evaluates activities such as sitting, rolling, lying down, sitting up, kneeling, head lifting, standing, jumping, or using stairs
- Each activity is scored on a scale ranging from 0 to 2
  - 0: unable to perform
  - 1: performed with modification
  - 2: performed without modification
- Total scores range from 0 to 66 points, with an increase in total score indicating motor function improvements

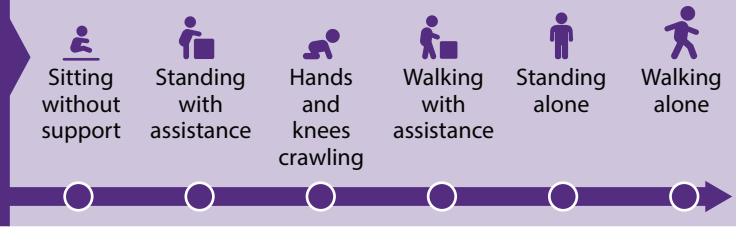
Other assessments

Revised Upper Limb Module (RULM)

- Scoring system designed to evaluate arm function in people with SMA
- Evaluates arm and hand activities such as manipulating, moving items, and raising arms
- Total scores range from 0 to 37, with higher scores indicating better arm function

World Health Organization (WHO) Developmental Milestones

- Scoring system designed to evaluate motor function
- Evaluates achievement of 6 age-appropriate motor milestones:



SMA: Spinal muscular atrophy

Note that the researchers assessed the effects of apitegromab on motor function, which is what patients with SMA perceive as the important constraint of the disorder. They did not measure the actual size or strength of patients' muscles before or after treatment. Equally important in this trial, researchers evaluated the safety of apitegromab by recording the most common side effects and whether any serious side effects (major health problems) occurred throughout the trial.

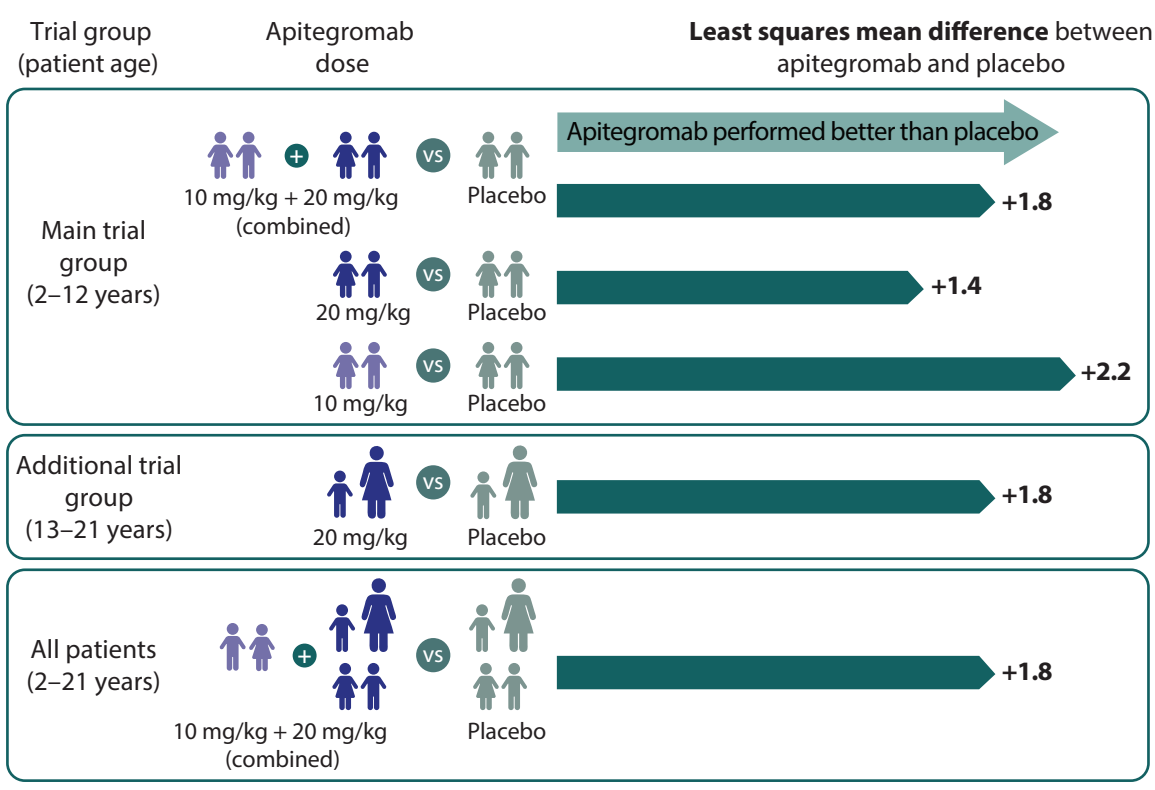
What were the overall results of the trial?

- Overall, patients receiving apitegromab had consistently better changes in motor function than patients receiving placebo after 1 year.
- Throughout the trial, the side effects were similar between patients who received either apitegromab or placebo. They were also typical for people living with SMA and those receiving an SMN-targeted treatment.

1 Did treatment with apitegromab improve motor function?

Based on Hammersmith Functional Motor Scale-Expanded (HFMSE) scores, the overall changes in motor function were better in patients receiving apitegromab and SMN-targeted treatment compared with patients receiving placebo and SMN-targeted treatment.

Difference between apitegromab and placebo in (Hammersmith Functional Motor Scale-Expanded) score change



Overall, the average difference in HFMSE score was
1.8 points higher in favor of apitegromab
vs placebo at 1 year in the main trial group

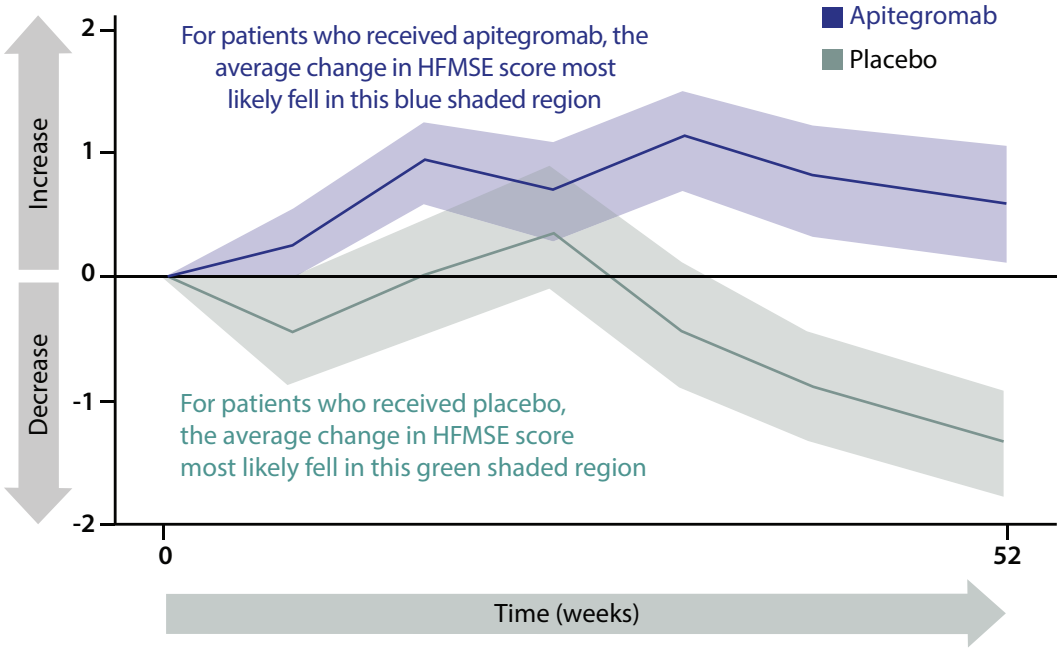
Least squares mean change: This is a way that researchers measure the average amount of change in something (e.g. motor function score changes, blood pressure, weight, pain level, etc.) while taking other factors into account such as age, other treatments, or starting values. The result is a fair average that helps compare study groups.

After analyzing the data, the 1.8-point difference between treatment groups was **statistically significant**, which means that the outcomes are likely real and not due to random chance. This is the best possible evidence to show that apitegromab treatment was truly effective. While the implications of improving on the HFMSE assessment may vary between patients, improving by a single point in one or several HFMSE-related tasks could be considered **clinically meaningful** for patients living with SMA type 2 or 3. People with SMA tend to be very skilled at using the muscle power they have to accomplish things, and at any level, a little bit more makes a difference. This is especially true if the small improvements translate to being able to sit without assistance, reach for objects, or perform self-care activities independently.

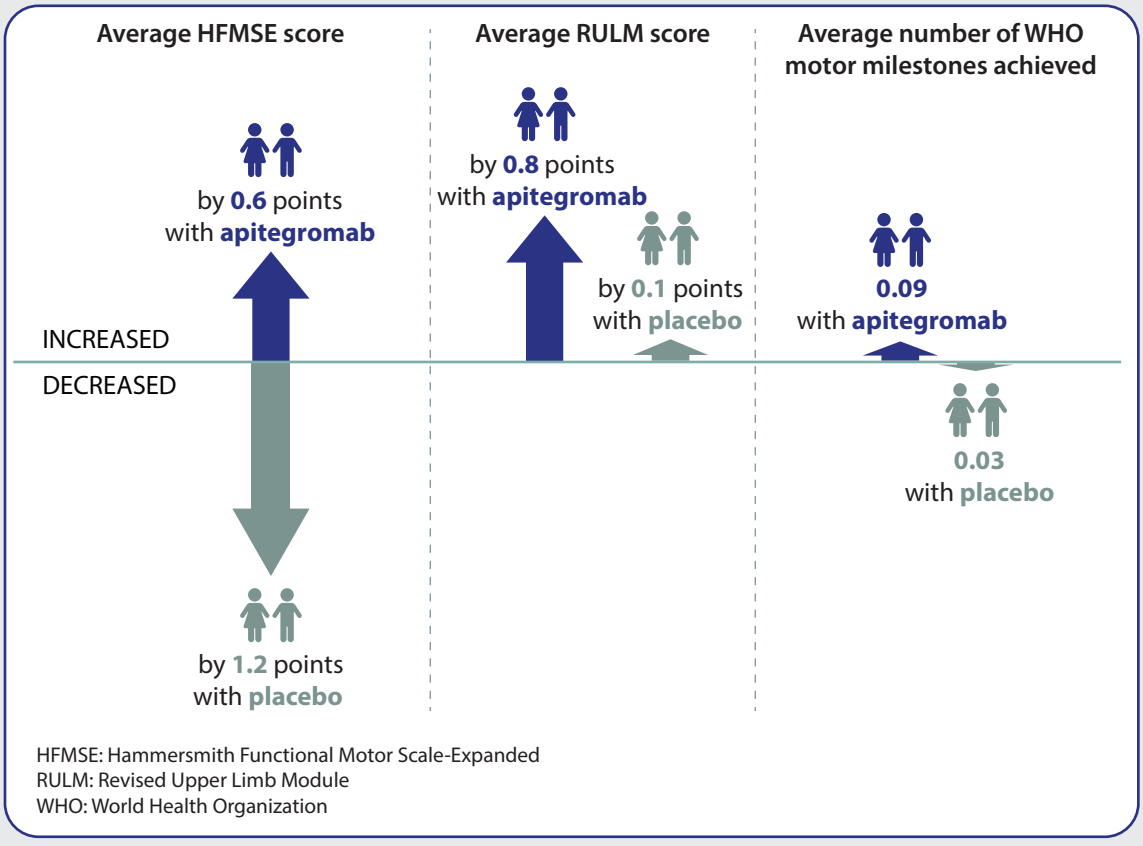
Statistical significance: Indicates the observed outcomes or differences between two groups are unlikely to be explained by random chance. In research, significant differences carry more weight than simple numeric differences.
Clinically meaningful change: Maintenance or small improvements in motor function that lead to better quality of life or independence for patients – especially if they add to earlier progress or happen during a time when motor function would normally decline.

In the main trial group (aged 2–12 years), improvements in HFMSE scores were seen as early as 2 months after beginning treatment with apitegromab:

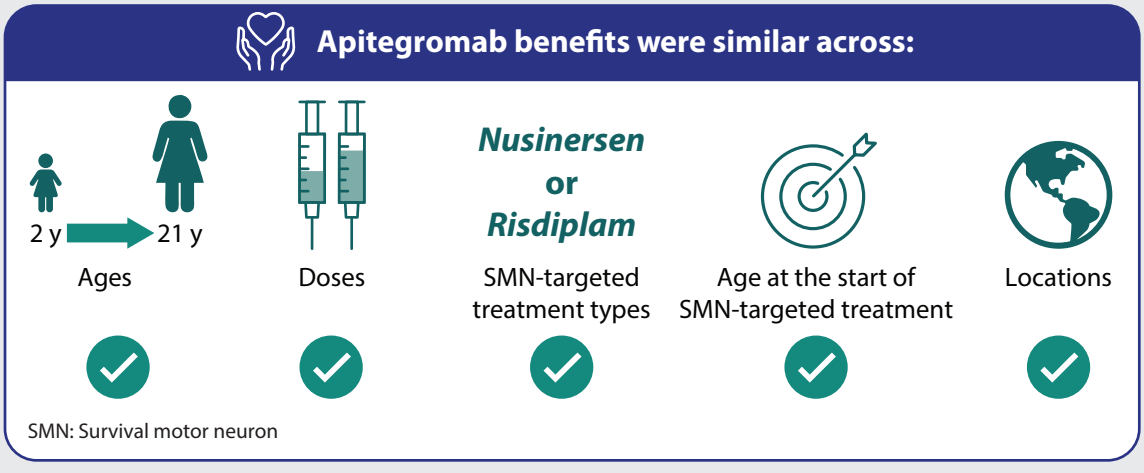
Change in Hammersmith Functional Motor Scale-Expanded (HFMSE) total score after the start of the trial (main trial group aged 2–12 years)



Although all patients were receiving SMN-targeted treatments, overall changes in motor function in the main trial group (aged 2–12 years) after 1 year were greater among patients receiving apitegromab.

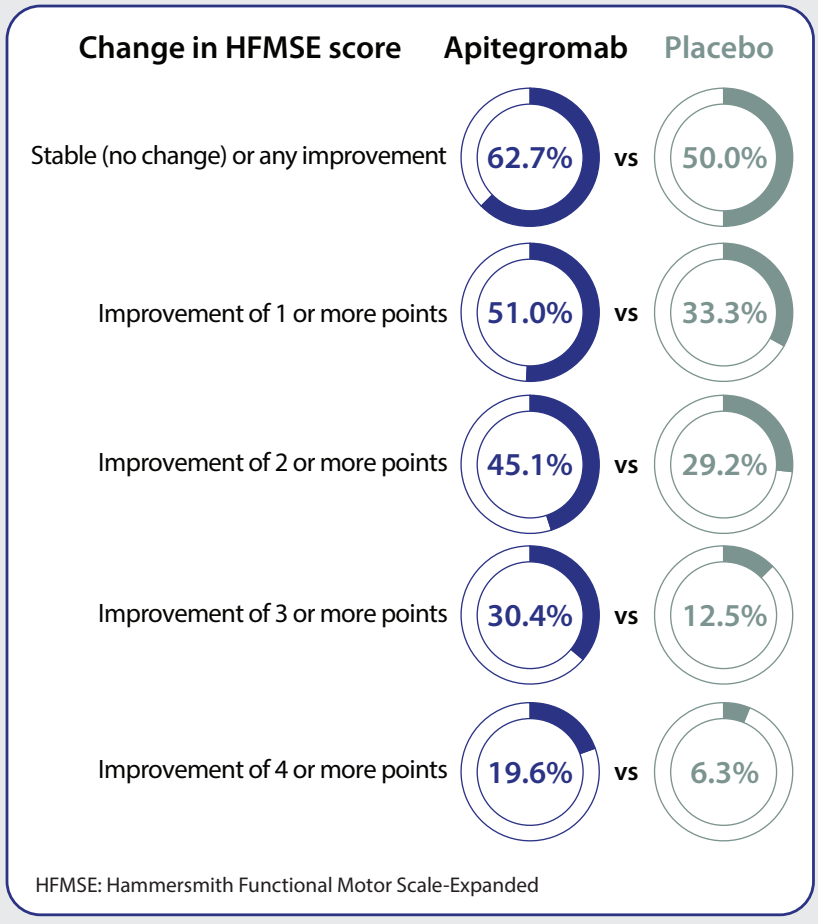


Apitegromab worked well for patients no matter their age, the dose they received, the type of SMN-targeted treatment they were on (nusinersen or risdiplam), the age they started SMN-targeted treatment, or where they lived (North America or Europe).



2 What percentage of patients had improvement in motor function?

In the main trial group (aged 2–12 years), the percentages of patients who had stable or improved HFMSE scores after 1 year of treatment were:



HFMSE: Hammersmith Functional Motor Scale-Expanded

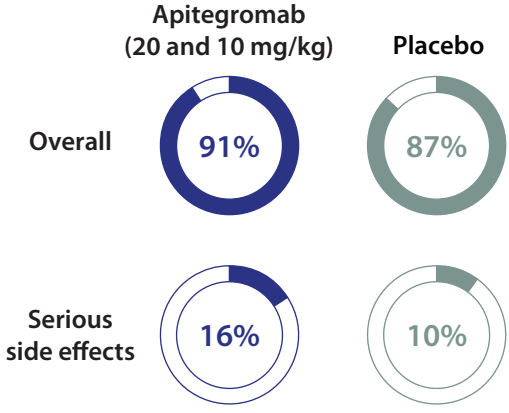
A higher percentage of patients receiving apitegromab and SMN-targeted treatment saw stabilization or improvements in their motor function compared with patients receiving placebo and SMN-targeted treatment, across all point categories. Particularly, the percentage of patients achieving at least a 3-point improvement in their HFMSE scores were greater among the patients treated with apitegromab (30.4%) compared to placebo (12.5%). Overall, patients treated with apitegromab were approximately 3 times more likely to improve and achieve an increase of 3 or more points in HFMSE score after 1 year of treatment.

3 What were the safety findings of the trial?

Researchers recorded all side effects experienced by any of the 188 trial patients at any time during the 1-year treatment period. A similar percentage of patients treated with apitegromab or placebo experienced one or more side effects (91% receiving apitegromab and 87% receiving placebo, overall) or any serious side effects (16% receiving apitegromab and 10% receiving placebo, overall). Overall, side effects were consistent with symptoms of SMA or ongoing SMN-targeted treatment. Altogether, the incidence (rate) of mild and severe side effects were generally similar between the apitegromab and placebo groups. None of the side effects that were considered serious or led patients to stop treatment or leave the trial were deemed to be related to receiving apitegromab or placebo (**'treatment-related'**).

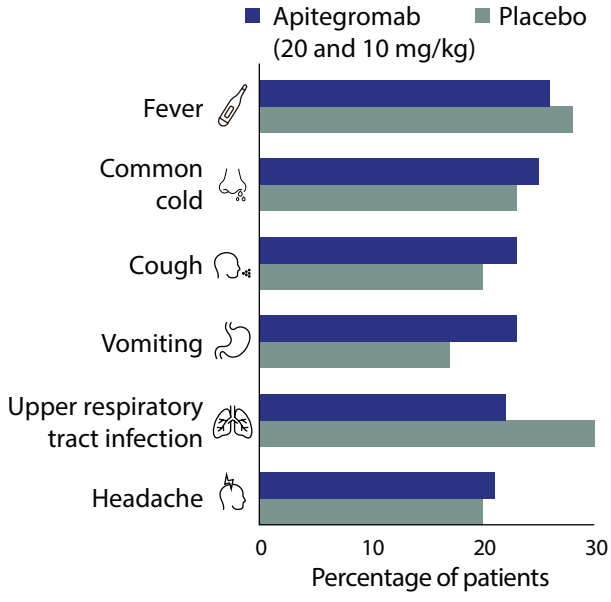
Treatment-related side effect: An unintended, undesirable effect thought to occur as a result of a treatment.

Incidence of side effects (trial group aged 2–21 years)



There were no:
- Side effects of special interest
- Deaths
- Study drug withdrawals due to side effects

Most common side effects (trial group aged 2–21 years)



Moderate increases in creatine kinase, a protein found in muscles, were observed in blood samples taken from patients treated with apitegromab. Although increased levels of creatine kinase in the blood could indicate muscle damage, moderate increases are common in people living with SMA. Because there were no side effects related to the increased creatine kinase, the levels observed may reflect increased physical activity or motor function rather than a safety concern.

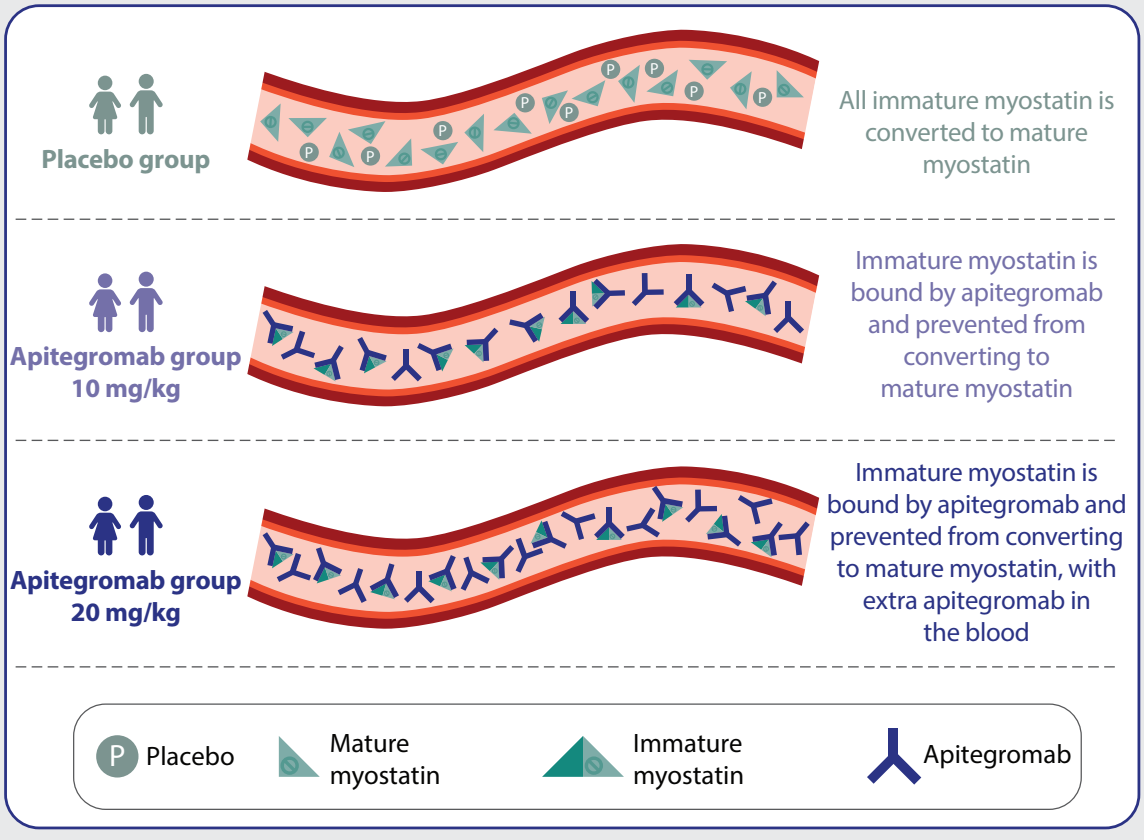
At the end of the trial, all but three patients chose to receive apitegromab in the long-term extension trial, suggesting that apitegromab was well tolerated.

4 What happens to apitegromab in the body?

Patients were given doses of apitegromab every month for a year. Apitegromab levels in the bloodstream stayed steady over the year of treatment. Patients who received the higher dose had higher levels of apitegromab in the blood compared with those who received the lower dose.

5 How did apitegromab affect myostatin?

Apitegromab increased blood levels of total nonfunctional immature myostatin, and both the higher and lower doses raised it to a similar degree. This means that apitegromab was working as intended, keeping myostatin in its inactive, immature form. In contrast, no increase in this immature form of myostatin was seen in patients receiving placebo. The outcome was expected as the placebo treatment does not prevent the conversion of immature myostatin to mature myostatin.



Sometimes a person's immune system recognizes a drug as something 'foreign' and makes antibodies against the drug. These are called 'antidrug antibodies'. In some situations, antidrug antibodies can cause the drug to be removed by the immune system from the body sooner than expected. In SAPPHIRE, one participant developed antidrug antibodies against apitegromab; however, the antidrug antibodies did not seem to have an effect on the blood levels of apitegromab, how apitegromab bound latent myostatin, or the effectiveness and safety of apitegromab.

What do the results of the SAPPHIRE trial mean?

The results of SAPPHIRE indicate that apitegromab treatment can improve motor function in people with SMA, aged 2–21 years who are receiving an SMN-targeted treatment. Prior to enrolling in SAPPHIRE, patients' duration of SMN-targeted treatment ranged from 1 to 11 years, suggesting that apitegromab can enhance motor function regardless of whether someone has just started SMN-targeted treatment or they have been receiving SMN-targeted treatment for several years or more. Apitegromab has the potential to transform the treatment of SMA by directly addressing muscle atrophy to improve motor function. For people living with SMA, small improvements in motor function can have substantial benefits in quality of life.

Because safety findings, motor function improvements, and effects on latent myostatin levels were similar with both doses of apitegromab, the researchers concluded that the lower 10 mg/kg dose may represent the optimal dose for stabilizing or improving motor function in people living with SMA who are also receiving an SMN-targeted treatment.

What were the limitations of the SAPPHIRE study?

There are a few limitations to keep in mind when looking at the SAPPHIRE trial results. Patients with severe contractures or scoliosis, less than 2 years of age, or had extreme muscle weakness, were not included in the trial as these factors could affect measurement of motor abilities. This trial also did not include patients who were able to walk independently. As such, the impact of apitegromab treatment for patients who fell outside the eligibility criteria remains to be evaluated.

Are there any plans for future clinical trials of apitegromab?

Patients who completed 1 year of treatment with apitegromab or placebo in SAPPHIRE were offered the option to enroll in ONYX, a phase 3 extension trial intended to evaluate the longer-term safety and efficacy of apitegromab. ONYX is an ongoing, open-label trial, meaning that trial patients and researchers know that all patients are receiving apitegromab. An additional phase 2 trial, OPAL, is planned to evaluate the effectiveness and safety of apitegromab in children under 2 years of age with SMA who are receiving nusinersen or risdiplam or who have previously received gene therapy for SMA.

Where can I find more information?

SAPPHIRE
The original article title is 'Efficacy and safety of apitegromab in nonambulatory type 2 or 3 spinal muscular atrophy (SAPPHIRE): a phase 3, double-blind, randomized, placebo-controlled trial.' It can be found at: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(25)00225-X/abstract

Citation: Crawford TO, Servais L, Mercuri E, *et al.* Efficacy and safety of apitegromab in nonambulatory type 2 or 3 spinal muscular atrophy (SAPPHIRE): a phase 3, double-blind, randomized, placebo-controlled trial. *Lancet Neurol.* 2025; 24 (9):727-739. doi: 10.1016/S1474-4422(25)00225-X.

Trial registration site: https://clinicaltrials.gov/study/NCT05156320
Study start date: April 14, 2022
Study end date: September 4, 2024

Additional studies investigating apitegromab:

TOPAZ
Published results:
'Safety and Efficacy of Apitegromab in Patients With Spinal Muscular Atrophy Types 2 and 3.' It can be read for free at: https://www.neurology.org/doi/10.1212/WNL.0000000000209151

'Long-term efficacy, safety, and patient-reported outcomes of apitegromab in patients with spinal muscular atrophy: results from the 36-month TOPAZ study.' It can be read for free at: https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2024.1419791/full

Trial registration site: https://clinicaltrials.gov/study/NCT03921528

ONYX
Trial registration site: https://clinicaltrials.gov/study/NCT05626855

Additional educational resources
https://www.lifetakesmuscle.com/

Additional background information on SMA and SMA treatments cited in this article
Wirth B, *et al. Ann Rev Genom Hum Genet*. 2020;21:231–261. It can be read for free at: https://www.annualreviews.org/content/journals/10.1146/annurev-genom-102319-103602

Acknowledgements
The authors thank the SAPPHIRE trial patients, their families, and the trial site personnel. Project management support was provided by T Bosquez-Berger, PhD, of Scholar Rock, Inc.

Disclosure statement
TO Crawford is the lead principal investigator of the Scholar Rock Inc sponsored phase 2 TOPAZ trial and a consultant and/or advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, and Roche/Genentech. L Servais has received grants and personal fees from AveXis/Novartis Gene Therapies, Biogen, and Roche and personal fees from Biohaven, Cytokinetics, and Scholar Rock, Inc., outside the submitted work. E Mercuri has received personal compensation for clinical trial consulting and serves on scientific advisory boards and research funding from Novartis Gene Therapies. H Kölbel serves on a scientific advisory board for AveXis and receives travel expenses and speaker honoraria from Biogen, Pfizer, Roche, and Sanofi. N Kuntz serves on medical advisory boards for Argenx, Biogen, Novartis, Roche, Sarepta, and Scholar Rock, Inc. Her institution receives research funds from Argenx, Astellas, Biogen, Catalyst, Novartis, Sarepta, and Scholar Rock, Inc. RS Finkel has received personal compensation for consulting and for advisory board participation from Biogen, Novartis, Novartis Gene Therapies, Roche, and Scholar Rock, Inc.; editorial fees from Elsevier for coediting a neurology textbook; license fees from the Children's Hospital of Philadelphia; and research funding from Biogen, Novartis Gene Therapies, Roche/Genentech, and Scholar Rock, Inc. J Krueger is a site principal investigator for AveXis/Novartis Gene Therapies, Biohaven, FibroGen, Roche/Genentech, and Scholar Rock, Inc., and serves as a Data and Safety Monitoring Board member for Astellas. K Batley receives research support from Biogen, Elpida, FibroGen, Novartis, NS Pharma, PTC Therapeutics, Regenxbio, ReveraGen, Sarepta Therapeutics, Scholar Rock, Inc., and Cure SMA. She has served on medical advisory boards for Biogen, Catalyst, Pfizer, PTC Therapeutics, Reata Pharmaceuticals, Sarepta Therapeutics, and UCB. S Dunaway Young has been a member of advisory boards for Biogen, Roche/Genentech, and Scholar Rock, Inc.; received personal compensation for activities with Biogen, Cure SMA, and Scholar Rock, Inc., as a consultant; and received research support from Cure SMA and the SMA Foundation. JL Marantz, G Song, B Yao, G Zhao, J Rossello, and G Tirucherai are Scholar Rock Inc employees and stockholders. ES Mazzone has received consulting fees from Biogen, Novartis, Roche, and Scholar Rock, Inc. RJ Butterfield receives funding via contracts for clinical trials from AveXis, Biogen, Pfizer, PTC Therapeutics, and Sarepta Therapeutics. He serves on scientific advisory boards for AveXis, Biogen, Pfizer, and Sarepta Therapeutics. M Gomez Garcia de la Banda serves as a scientific advisory board member for Biogen, Novartis Gene Therapies, and Roche. VA Sansone serves as a scientific advisory board member for Biogen, Novartis, Roche, and Sarepta. L De Waele has received grant funding from the Belgian Government of Health and grant funding and honoraria for advisory board meetings, lectures, and travel expenses from Baxter, B. Braun, Cardinal Health, Danone-Nutricia, and Fresenius Kabi. WL van der Pol receives research support from the Prinses Beatrix Spierfonds, and Stichting Spieren voor Spieren. His employer receives fees for consultancy services to AveXis, Biogen, Biohaven, NMD Pharma, Novartis, Roche, and Scholar Rock, Inc. He was involved as an investigator at a participating centre in trials on the safety and efficacy of olesoxime for children with SMA types 2 and 3a (NCT02628743) and is involved as an investigator of the mono-centre placebo-controlled trial on pyridostigmine in children and adults with SMA types 2-4 (SPACE 2014). C Cances is a site principal investigator for Biogen, Novartis Gene Therapies, and Roche clinical trials, serves as a scientific advisory board member for Novartis Gene Therapies, Roche, and Pfizer,

and has received advisory fees from Roche and Pfizer. Astrid Pechmann has received compensation for advisory boards, training activities and research grants from Biogen and Novartis. BT Darras has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Merck, Roche/Genentech, Sarepta Therapeutics, and Scholar Rock, Inc.; steering committee member for Roche FIREFISH and MANATEE studies; and Data and Safety Monitoring Board member for Amicus Inc., ArgenXBV, and Lexeo Therapeutics; he has no financial interests in these companies. He has received research support from the National Institutes of Health/National Institute of Neurological Disorders and Stroke, the Spinal Muscular Atrophy Foundation, CureSMA, and has received grants from Ionis Pharmaceuticals, Inc., for ENDEAR, CHERISH, CS1/CS2/CS12 studies, from Biogen for CS11 and ASCEND studies, and from Fibrogen, Novartis (AveXis), PTC Therapeutics, Roche, Sarepta Therapeutics, and Scholar Rock, Inc. He has also received royalties for books and online publications from Elsevier and Wolters Kluwer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing, graphical concepts, and editorial support were provided by K Corcoran, PhD, A Moriarty, PhD, N Farra, PhD, and S Davis of Apollo Medical Communications, part of Helios Global Group, and funded by Scholar Rock, Inc.

Patient reviewers on this PLSP have received honorarium from [journal name] for their review work but have no other relevant financial relationships to disclose.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This Plain Language Summary of Publication was funded by Scholar Rock, Inc.

ORCID details

Thomas O. Crawford	0000-0003-0916-2797
Laurent Servais	0000-0001-9270-4061
Eugenio Mercuri	0000-0002-9851-5365
Nancy Kuntz	0000-0003-2253-5156
Richard S. Finkel	0000-0002-9351-7054
Kaitlin Batley	0000-0002-6394-7432
Sally Dunaway Young	0000-0001-9322-0608
Elena Stacy Mazzone	0000-0002-7857-5600
Russell J. Butterfield	0000-0002-8452-7189
Marta Gomez Garcia de la Banda	0000-0002-2252-0694
Valeria A Sansone	0000-0002-1354-3800
Liesbeth De Waele	0000-0001-7126-575X
Claude Cances	0000-0001-7386-2275
Basil T. Darras	0000-0002-1536-8145

Author affiliations

[a]Departments of Neurology and Pediatrics, Johns Hopkins Medical, Baltimore, MD, USA; [b]Department of Pediatrics, MDUK Oxford Neuromuscular Centre and NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK; Department of Paediatrics, Neuromuscular Reference Centre, University Hospital of Liège, Liège, Belgium; [c]Centro Clinico NeMO, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Neuropsichiatria Infantile Paediatric Neurology Unit, Catholic University, Rome, Italy; [d]Department of Pediatric Neurology, Centre for Neuromuscular Disorders, Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, Essen, Germany; [e]Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [f]Center for Experimental Neurotherapeutics, St. Jude Children's Research Hospital, Memphis, TN, USA; [g]Helen DeVos Children's Hospital Neurology-Grand Rapids, Grand Rapids, MI, USA; [h]Department of Pediatrics and Neurology, University of Texas Southwestern Medical Center, Dallas, TX, USA; Department of Pediatrics and Neurology, Children's Medical Center Dallas, Dallas, TX, USA; [i]Departments of Neurology and Clinical Neurosciences, Stanford University, Palo Alto, CA, USA; [j]Scholar Rock, Inc., Cambridge, MA, USA; [k]Catholic University, Rome, Italy; [l]Department of Pediatrics and Neurology, University of Utah, Salt Lake City, UT, USA; [m]Assistance Publique Hôpitaux de Paris, Sorbonne Université, Institut de Myologie, AFM-Telethon, Essais cliniques I-Motion Enfants, Hôpital Armand Trousseau, F-75012 Paris, France; [n]The NeMO Clinical Center, Neurorehabilitation Unit, University of Milan, Milan, Italy; [o]Department of Paediatrics, University Hospitals Leuven, Leuven, Belgium; Department of Development and Regeneration, KU Leuven, Leuven, Belgium; [p]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Netherlands; [q]Department of Paediatric Neurology, Reference Centre for Neuromuscular Disorders AOC, and Paediatric Clinical Research Unit Children's Hospital, Toulouse University Hospital Center, Toulouse, France; [r]Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [s]Department of Neurology, Neuromuscular Program, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
*A complete list of the investigators in the SAPPHIRE Study Group is provided in the supplementary appendix to the original article, which is linked in the 'Where can I find more information?' section of the article