NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the effects and safety of AVXS-101 in babies with SMA type 1

Protocol number: AVXS-101-CL-302 or COAV101A12301

Thank you!

AveXis, a Novartis company, sponsored this trial and would like to thank the parents and their babies for taking part in this trial to study the **treatment AVXS-101, also known as onasemnogene abeparvovec-xioi**. You helped researchers learn more about how AVXS-101 works in babies with **spinal muscular atrophy (SMA) type 1**.

Your invaluable contribution to medicine and healthcare is greatly appreciated.

This summary only shows the results of one clinical trial. Other clinical trials may have different findings. Researchers and health authorities, such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), look at the results of many clinical trials to understand which treatments work and if they are safe. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Why was the research needed?

Researchers are looking for a way to treat **spinal muscular atrophy**, also called **SMA**. SMA is a group of conditions that cause the body to lose **motor neurons**. Motor neurons are the nerve cells in the spinal cord that control muscle movement in the arms, legs, chest, face, throat, and tongue. In SMA, the motor neurons die and can't tell the muscles how to work. The muscles become weak and cause problems with:

- Moving parts of the body
- Breathing
- Swallowing

Babies are born with **SMA type 1** and symptoms usually start before they are 6 months old. Without treatment, many babies with SMA type 1 cannot hold their head up or sit up, and may not live past age 2.

SMA type 1 is caused by a missing or nonworking survival motor neuron 1 (*SMN1*) gene. *SMN1* is needed for motor neurons to live. When the *SMN1* gene isn't working, motor neurons die and can't control muscles.

What was the purpose of this trial?

The main purpose of this trial was to learn more about the safety and effects of AVXS-101 in babies with SMA type 1, including effects on their ability to sit up on their own, which is a key milestone in child development. **AVXS-101** is a gene therapy designed to treat babies with SMA type 1. **Gene therapy** is a treatment that corrects or replaces the missing or nonworking gene to treat disease. When this trial started, AVSX-101 was not approved in any countries to treat SMA type 1. While this trial was taking place, AVXS-101 was approved in the U.S. and in other countries to treat babies with SMA type 1.

A past clinical trial of AVXS-101 showed that some babies with SMA type 1 lived longer and had better muscle strength after treatment. This trial was also designed to confirm these results.

The main questions the researchers wanted to answer in this trial were:

- How many of the babies could sit up without help for 10 seconds at least once by 18 months of age?
- What medical problems did the babies have during the trial?

Another question the researchers wanted to answer was:

- How many of the babies were alive and did not need permanent ventilation at 14 months of age?

Trial treatment

The treatment given in this trial was:

AVXS-101, also known as **onasemnogene abeparvovec-xioi**, which was given once through a vein as a one-hour intravenous (IV) infusion.

How long was this trial?

This trial started in August 2018 and ended in September 2020. It was designed so that each baby would receive treatment before they were 6 months old and have follow-up visits until they were 18 months old. The researchers completed this trial as planned. When the trial ended, the researchers collected information on the trial treatment and created a report of the trial results. This summary is based on the report.

Who was in this trial?

33 babies with SMA type 1 took part in this trial. There were 19 girls and 14 boys. When they joined the trial, the babies were between the ages of 2 and 6 months, with an average age of 4 months.

They took part at 10 hospital sites in Belgium, France, Italy, and the United Kingdom.

What kind of trial was this?

This was an open-label trial, which meant that the parents and the clinical trial team knew that the babies received AVXS-101.

What happened during this trial?

Up to one month

During screening

After the babies' parents gave their written consent, trial doctors checked the babies' health to make sure they could be in this trial. The babies could take part if they:

- Had SMA type 1 based on genetic test results
- Were able to swallow or were receiving feeding support
- Could usually breathe without help or with some help from a breathing machine
- Had no other serious health problems

1 dose

During treatment

The babies received AVXS-101 as one IV infusion which lasted about one hour.

After receiving the IV infusion, they stayed with their family at the hospital site for 2 days so the researchers could closely check their health.

Until 18 months old

During follow-up

The babies had many follow-up visits for trial doctors to check their health until they were 18 months old. During the COVID-19 pandemic, some visits were done by phone, video chat, or home visit. The researchers checked the babies' ability to sit up by themselves and their general health.

After the end of their follow-up visits, the researchers asked the parents if they wanted their babies to join a separate, long-term follow-up trial.

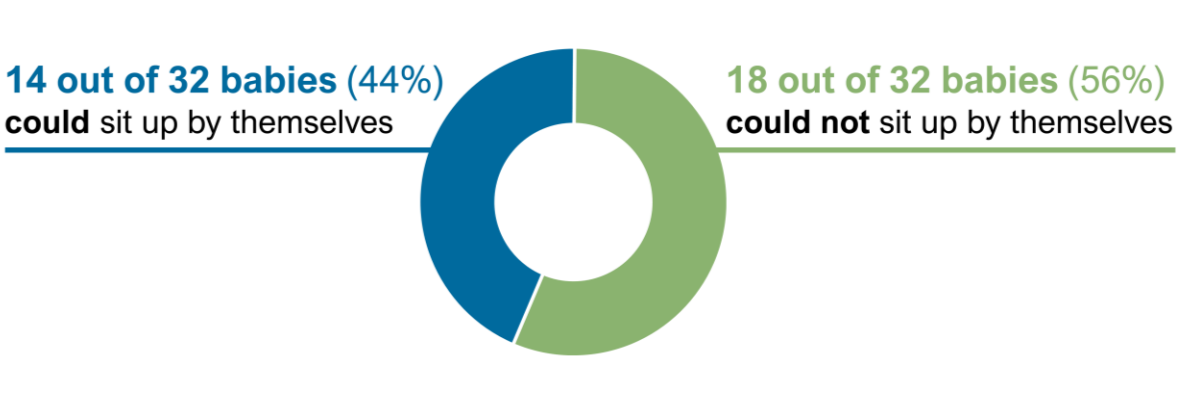
What were the main results of this trial?

How many of the babies could sit up without help for 10 seconds at least once by 18 months of age?

The trial staff took videos of the babies' ability to sit up at the trial visits. Each baby's parents could also take videos of their baby between visits and send them to the trial staff. The researchers kept track of how many babies could sit up without help for at least 10 seconds by 18 months of age.

By 18 months of age, 14 out of 32 babies (44%) could sit up without help at least once.

The number of babies who could sit up by themselves at least once before they turned 18 months old



Note: This figure does not include one baby who received AVXS-101 one day after turning 6 months old because they could not be compared to the other babies.

How did these results compare with babies who did not receive AVXS-101 in an earlier observational study?

The researchers compared these results to a past observational study of babies with SMA type 1. The comparison group included 23 babies who were also missing a working *SMN1* gene and received standard care because there was no SMA1 gene therapy available at the time.

In the comparison group, none of the 23 babies could sit up without help for 10 seconds. The clinical trial team concluded that AVXS-101 had a meaningful effect on the babies' ability to sit up in this trial.

How many of the babies were alive and did not need permanent ventilation at 14 months of age?

The trial staff kept track of how many babies were alive and did not need permanent ventilation at 14 months of age. **Permanent ventilation** is support with a breathing machine that either:

- Required tracheostomy (surgery to create a hole in the neck to connect the breathing tube to the windpipe)
- Was needed for at least 16 hours a day for 14 days in a row or longer

31 out of 32 babies (97%) were alive and did not need permanent ventilation at 14 months of age. In the past observational study, only 6 of the 23 babies (26%) were alive and did not need permanent ventilation at 14 months of age. The clinical trial team concluded that AVXS-101 had a meaningful effect on survival without permanent ventilation by 14 months of age in this trial.

What medical problems did the babies have during the trial?

Medical problems that happen in clinical trials are called "**adverse events**".

A lot of research is needed to know whether a treatment causes an adverse event. So, when new treatments are being studied, researchers keep track of all adverse events the participants have, whether or not they are thought to be caused by the trial treatment.

This section is a summary of the adverse events that happened during the trial. The websites listed at the end of this summary have more information about the adverse events that happened in this trial.

An **adverse event** is an unwanted sign or symptom that participants have during a trial. An adverse event is considered "**serious**" when it is causes lasting problems, needs hospital care to prevent serious problems, leads to or lengthens the need for hospital care, or leads to death. These problems may or may not be caused by the trial treatment.

What were the most common serious adverse events?

19 babies had serious adverse events. One baby died during the trial from problems due to a respiratory tract infection related to their SMA type 1.

Serious adverse events that happened in at least 3 out of 33 babies (9% of babies):

	AVXS-101
	Number out of 33 babies (percent %)
Lung infection Pneumonia	**5 babies** (15%)
Fever Pyrexia	**4 babies** (12%)
Diarrhea and throwing up Gastroenteritis	**3 babies** (9%)
Infection in the nose, throat, airways, or lungs Respiratory tract infection	**3 babies** (9%)
Infection in the nose, throat, and airways Upper respiratory tract infection	**3 babies** (9%)

What were the most common non-serious adverse events?

32 babies had adverse events that were not considered serious.

Non-serious adverse events that happened in at least 8 out of 33 babies (24% of babies):

	AVXS-101
	Number out of 33 babies (percent %)
Fever Pyrexia	**20 babies** (61%)
Infection in the nose, throat, and airways Upper respiratory tract infection	**10 babies** (30%)
Throwing up Vomiting	**8 babies** (24%)
Possible signs of liver damage based on lab tests	
Alanine aminotransferase increased	**9 babies** (27%)
Aspartate aminotransferase increased	**8 babies** (24%)
Hypertransaminasaemia	**8 babies** (24%)

How has this trial helped?

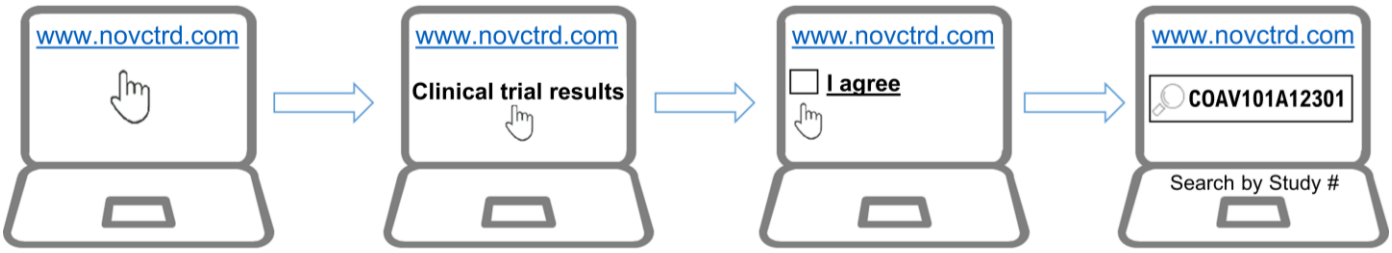
This trial helped researchers learn more about how well AVXS-101 works and if it is safe to use in babies with SMA type 1. The clinical trial team concluded that the babies were more likely to be able to sit up by 18 months of age compared to babies in a past observational study who did not receive the trial treatment. The babies in this trial were also more likely to be alive and not need permanent ventilation at 14 months of age compared to babies in the observational study. The researchers also found there were no new safety concerns for the babies in this trial.

During this trial, the European Medicines Agency (EMA) conditionally approved AVXS-101 to treat babies with SMA type 1 up to age 2 in May 2020. Conditional approval means the EMA approved AVXS-101 for use in babies for one year, and the EMA reviews again after one year. Conditional approval was based on available clinical trial data that this gene therapy treats an unmet medical need and the benefit to patients is greater than the risk of waiting for more data. At the end of each year of conditional approval, the EMA reviews more clinical trial data and decides to either renew conditional approval or grant full approval. The results from this trial were submitted to the EMA as part of their review.

Please remember, this summary only shows the results of one clinical trial. Other clinical trials may have different results. Researchers and health authorities look at the results of many clinical trials to understand which treatments work and if they are safe. It takes many people in multiple clinical trials around the world to advance medical science and healthcare. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com).



You can find more information about this trial on these websites:

- www.clinicaltrials.gov. Use the NCT identifier **NCT03461289** in the search field.
- www.clinicaltrialsregister.eu. Use the EudraCT identifier **2017-000266-29** in the search field.

Full clinical trial title: Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion

Thank you

Thank you to the babies and their parents for taking part in this trial. As a clinical trial participant, your baby and you belong to a large community of participants around the world. You helped researchers answer important health questions and test new medical treatments.

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Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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