NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the effects and safety of AVXS-101 in babies who had SMA but no symptoms

Clinical trial protocol number: AVXS-101-CL-304 or COAV101A12303

Thank you!

Thank you to the parents and their babies who took part in the clinical trial for the **treatment AVXS-101,** also known as **onasemnogene abeparvovec**.

All of the parents and babies helped the researchers learn more about how AVXS-101 works in people with **spinal muscular atrophy** (**SMA)**. AveXis, a Novartis company, sponsored this clinical trial and believes it is important to share what was learned from the results of this trial with the participants and the public.

We hope this helps the parents and babies understand their important role in medical research.

? **If your baby was a participant and you have any questions about the results, please talk to the doctor or staff at the trial site.**

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings.

Why was the research needed?

Researchers are looking for better ways to treat **spinal muscular atrophy**, also called **SMA**. SMA is a group of conditions that causes 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

SMA 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.

Copies of a similar gene called ***SMN2*** can help make up for a nonworking *SMN1* gene. People can have up to 5 copies of the *SMN2* gene. People with more copies of the *SMN2* gene often have more mild symptoms that start later in life.

AVXS-101 is a gene therapy designed to treat babies with SMA by correcting the missing or nonworking *SMN1* gene. **Gene therapy** is a treatment that corrects or replaces a missing or nonworking gene to treat disease. When this trial started, AVXS-101 was not approved in any countries to treat SMA. 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.

Trial purpose

The main purpose of this trial was to learn about the effects and safety of AVXS-101 when given to babies who had a genetic diagnosis of SMA with either 2 copies or 3 copies of the *SMN2* gene but did not have any symptoms of SMA.

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

- How many babies with 2 copies of *SMN2* could sit up without help for at least 30 seconds by 18 months of age?
- How many babies with 3 copies of *SMN2* could stand up without help for 3 seconds by 24 months of age?
- What medical problems did the babies have during the trial?

Trial treatment

The treatment given in this trial was:

AVXS-101, which was given once through a vein as a one-hour intravenous (IV) infusion.

How long was this trial?

The trial started in April 2018 and ended in June 2021. It was designed so that each baby would receive treatment when they were up to 6 weeks of age and take part until they were up to 18 months (if they had 2 copies of *SMN2*) or 24 months of age (if they had 3 copies of *SMN2*).

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 that report.

Who was in this trial?

29 babies with a genetic diagnosis of SMA and 2 or 3 copies of *SMN2* were in this trial. None of the babies had any symptoms of SMA. The babies were up to 6 weeks of age at the time they received AVXS-101. Based on genetic testing, they had a missing or nonworking *SMN1* gene and either:

- 2 copies of the *SMN2* gene **(Group 1)**
- 3 copies of the *SMN2* gene **(Group 2)**

1 baby with a genetic diagnosis of SMA and 4 copies of the *SMN2* gene was enrolled into a planned, 3rd group (Group 3). After this baby joined, this group was cancelled. This summary shows the results of babies in Groups 1 and 2 and does not include the results of the baby in Group 3.

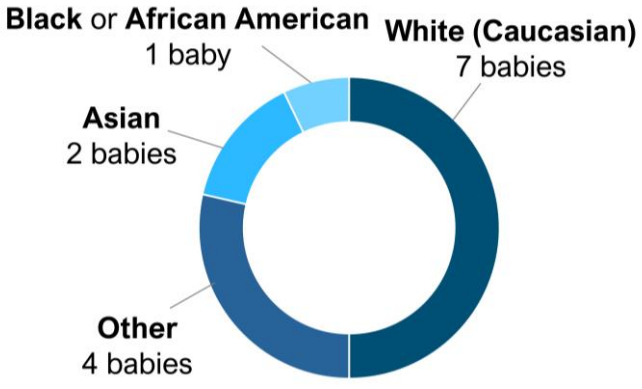
They took part at 16 hospital sites. The map below shows the number of babies who took part in each country.

Group 1

14 babies had 2 copies of the *SMN2* gene. Their ages at treatment ranged from 1 to 5 weeks. Their average age was 3 weeks.

The babies' genders were:

The babies' races were reported as:

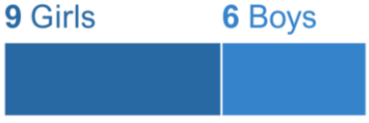


The ethnicity of 4 babies was reported as Hispanic or Latino.

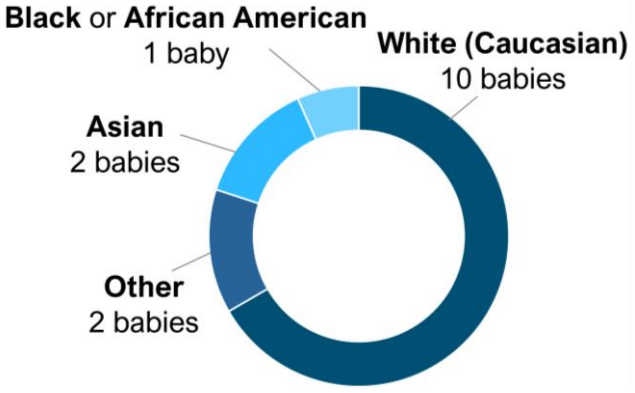
Group 2

15 babies had 3 copies of the *SMN2* gene. Their ages at treatment ranged from 1 to 6 weeks. Their average age was 4 weeks.

The babies' genders were:



The babies' races were reported as:



The ethnicity of 2 babies was reported as Hispanic or Latino.

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 1 month before treatment

During screening

Before starting treatment, trial doctors checked the babies' health and genetic test results to make sure they could be in this clinical trial.

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 for 2 days so the researchers could closely check their health.

Up to 24 months of age

During follow-up

After treatment, the babies had many follow-up visits for trial doctors to check their health until they were 18 months (Group 1) or 24 months of age (Group 2). During the COVID-19 pandemic, some visits were done by phone, video chat, or at a different site than planned. The researchers checked the babies' ability to sit or stand up by themselves and their general health.

One month after the baby's last visit, trial staff called them to check for any serious health problems.

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?

This is a summary of the overall results for 29 of the 30 babies, not including the baby in Group 3 who had 4 copies of *SMN2*. It does not show the results of each individual baby. Results of individual babies could be different from the results of the total group of babies. More details on the results can be found on the websites listed at the end of this summary.

How many babies with 2 copies of *SMN2* (Group 1) could sit up without help for at least 30 seconds by 18 months of age?

All 14 babies in Group 1 were able to sit up without help for at least 30 seconds by 18 months of age.

The number of babies who could sit up by themselves

To find this out, 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 30 seconds by 18 months of age.

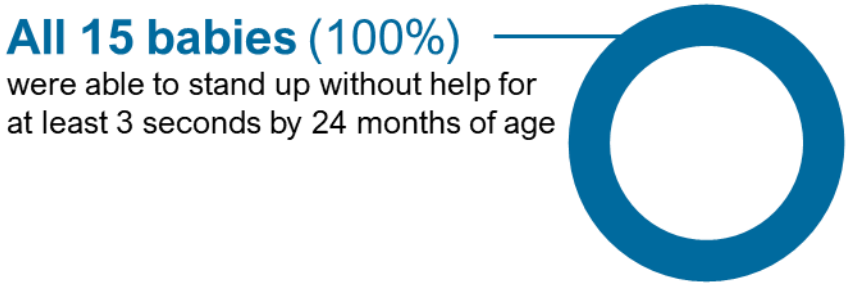
How did these results compare with babies who did not receive AVXS-101 in a past observational study?

The researchers compared these results to a past observational study of babies with SMA. The observational study was called the **Pediatric Neuromuscular Clinical Research (PNCR)** Network study. Based on the results from this study, babies with a genetic diagnosis of SMA and 2 copies of *SMN2* are never expected to sit without help. The researchers compared these results against the chance that none of the babies would be able to sit up without help. The clinical trial team concluded that AVXS-101 had a meaningful effect on the babies' ability to sit up in this trial.

How many babies with 3 copies of *SMN2* (Group 2) could stand up without help for 3 seconds by 24 months of age?

All 15 babies in Group 2 were able to stand up without help for at least 3 seconds by 24 months of age.

The number of babies who could stand up by themselves



To find this out, the trial staff took videos of the babies' ability to stand 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 stand up without help for at least 3 seconds by 24 months of age.

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

The researchers compared these results to babies with SMA in the past PNCR observational study . The PNCR comparison group included 81 babies who were also missing a working *SMN1* gene, had 3 copies of *SMN2*, and received standard of care because there was no *SMA* gene therapy available at the time.

In the PNCR comparison group, 19 of the 81 babies (24%) could stand up without help for 3 seconds. The clinical trial team concluded that AVXS-101 had a meaningful effect on the babies' ability to stand up in this trial.

What were the other results of this trial?

The researchers also looked at other possible effects of AVXS-101 for both groups and concluded that AVXS-101 had a meaningful effect on these measures.

What measures did researchers look at in Group 1?

The researchers kept track of how many of the babies were:

- Alive and did not need help breathing with **permanent ventilation** at 14 months of age
- Able to keep a normal weight without using a feeding tube at any point up to 18 months of age

All 14 babies in Group 1 were alive and did not need permanent ventilation at 14 months of age. 13 of the babies (93%) were able keep a normal weight without using a feeding tube up to18 months of age.

Permanent ventilation is breathing support with a 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 when not sick with another illness

What measures did researchers look at in Group 2?

The researchers kept track of how many babies were able to walk (take at least 5 steps without help) by 24 months of age. Of the 15 babies, 14 babies (93%) were able to take at least 5 steps by 24 months of age.

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 drug causes an adverse event. So, when new drugs 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 up to one month after the baby's last visit. 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 life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial treatment.

What were the serious adverse events?

There were no deaths reported during this trial. 8 babies had serious adverse events. The table below shows the **serious adverse events**.

	Group 1	Group 2
	Number out of 14 babies (percent %)	**Number out of 15 babies** (percent %)
Ear infection	**0** (0%)	**1** (7%)
Fluid buildup behind the eardrum Middle ear effusion	**1** (7%)	**0** (0%)
Kidney infection Pyelonephritis	**1** (7%)	**0** (0%)
Little to no energy and hard to wake up Lethargy	**0** (0%)	**1** (7%)
Part of the intestines bulges into the groin Inguinal hernia	**1** (7%)	**0** (0%)
A sleep disorder in which breathing repeatedly stops and starts Sleep apnea syndrome	**1** (7%)	**0** (0%)
Sore throat Pharyngitis	**0** (0%)	**1** (7%)
Too much calcium in the blood Hypercalcemia	**1** (7%)	**0** (0%)
Upper airway infection that causes a barking cough Croup infectious	**1** (7%)	**0** (0%)

What were the most common non-serious adverse events?

All 29 babies in Groups 1 and 2 had adverse events that were not considered serious.

The table below shows the **non-serious adverse events** that happened in 4 or more babies (more than 25%) in either group.

	Group 1	Group 2
	Number out of 14 babies (percent %)	**Number out of 15 babies** (percent %)
Fever Pyrexia	**7** (50%)	**11** (73%)
Infection in the nose, throat, and airways Upper respiratory tract infection	**5** (36%)	**9** (60%)
Frequent, loose, or watery stool Diarrhea	**3** (21%)	**4** (27%)
Possible sign of liver damage based on lab test Aspartate aminotransferase increased	**3** (21%)	**4** (27%)
Teeth start to come through gums Teething	**2** (14%)	**5** (33%)
Cough	**1** (7%)	**4** (27%)
Trouble passing stool Constipation	**4** (29%)	**1** (7%)

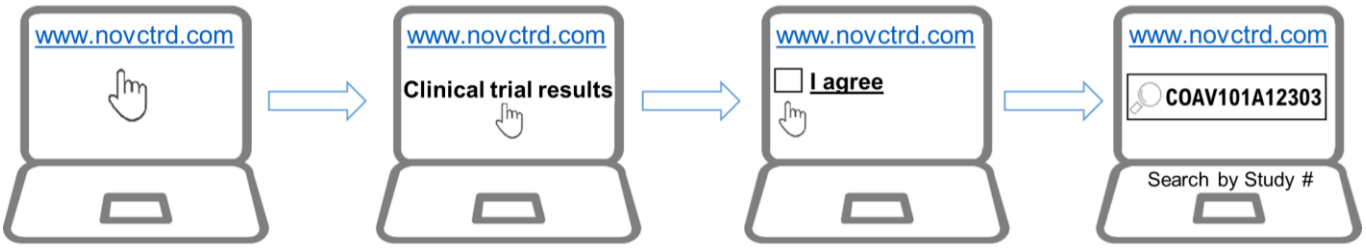
How has this trial helped?

This trial helped researchers learn more about how well AVXS-101 works and if it is safe to use in babies that were up to 6 weeks of age, who had a genetic diagnosis of SMA with 2 or 3 copies of the *SMN2* gene, but no symptoms of SMA at the time of treatment. Researchers concluded that the babies in this trial were more likely to be able to sit or stand up after receiving AVXS-101 before they had symptoms than would be expected for similar babies with SMA who didn't receive the treatment. Researchers also found no new safety concerns with AVXS-101.

Please remember, this summary only shows the results of this 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 drugs 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 **NCT03505099** in the search field.
- www.clinicaltrialsregister.eu. Use the EudraCT identifier **2017-004087-35** in the search field.

Full clinical trial title: A Global Study of a Single, One-Time Dose of AVXS-101 Delivered to Infants with Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy with Multiple Copies of *SMN2*.

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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