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Clinical Trial Results Summary

A clinical trial to learn about the effects and safety of giving AVXS-101 to babies and children with SMA as an injection in the lower back

Clinical trial protocol number: AVXS-101-CL-102 or COAV101A12102

Thank you!

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

All of the parents and children helped the researchers learn more about how AVXS-101 works in babies 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 child 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 a way to treat **spinal muscular atrophy**, also called **SMA**.

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. Without treatment, many babies with SMA are never able to walk.

What is 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

AVXS-101 is a gene therapy designed to treat babies and young children 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 country to treat SMA. While this trial was taking place, AVXS-101 was approved in the U.S. and other countries to treat babies with SMA type 1. It was approved to be given into a vein, which is called an intravenous (IV) infusion.

In this trial, researchers wanted to learn if giving AVXS-101 as an intrathecal injection could lower the chance of AVXS-101 damaging other organs, such as the liver, compared to IV infusions. An **intrathecal injection** means that doctors use a thin needle to inject AVXS-101 through the lower back and into the fluid below the end of the spinal cord.

Trial purpose

The main purpose of this trial was to learn about the safety and effects of different doses of AVXS-101 given as an intrathecal injection to babies and children with 3 copies of the ***SMN2* gene**, which includes **SMA types 2 and 3**. This included effects on their ability to stand up on their own and move.

The ***SMN2* gene** is similar to *SMN1* and can help make up for a nonworking *SMN1* gene.

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

- How many of the participants in the younger age group could stand up without help for 3 seconds at least once by a year after treatment?
- Could the participants in the older age group move more by a year after treatment?
- What medical problems did the participants have during the trial?

How long was this trial?

This trial started in December 2017 and ended in November 2021. This trial was designed so that each participant could take part for up to 17 months.

The researchers did not complete this trial as planned. This trial was designed to enroll up to 51 participants but ended after 32 participants had joined.

Why did this trial end early?

The FDA paused this trial's enrollment in October 2019 due to safety concerns found from an animal study using AVXS-101. After review of more safety data, the FDA allowed the trial to resume in August 2021, but the sponsor decided to not enroll more participants. This was because they had collected enough information to answer their research questions about the effects of AVXS-101 given as an intrathecal injection.

When the trial ended, the researchers collected information on the trial treatments and created a report of the trial results. This summary is based on that report.

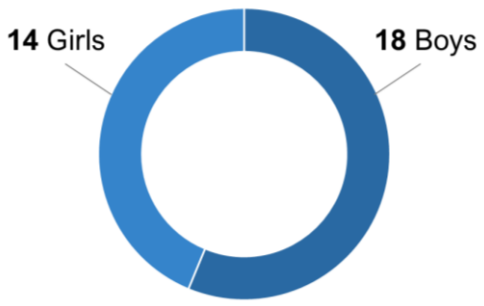
Who was in this trial?

32 participants with SMA were in this trial. Participants' ages ranged from 7 months to 4 and a half years. Their average age was 2 years.

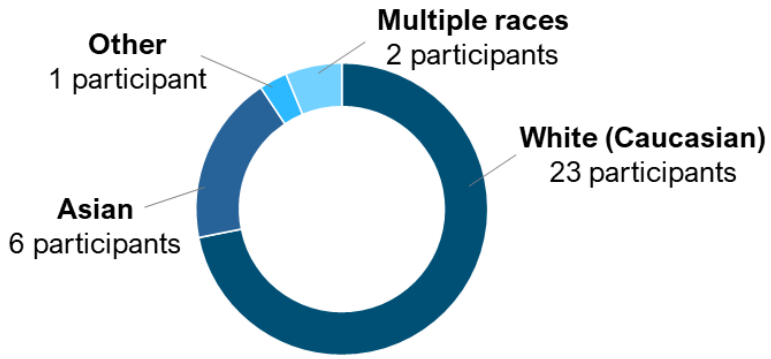
The participants were divided into **2 age groups**:

- **Younger age group:** 20 participants between ages **6 months and less than 2 years** when they received AVXS-101
- **Older age group:** 12 participants between ages **2 and less than 5 years** when they received AVXS-101

Participant gender



Participant race



5 participants' ethnicity was reported as Hispanic or Latino.

The participants could take part in this trial if they:

- Had SMA with **3 copies of the *SMN2* gene**, which includes **SMA types 2 and 3**
- Could sit up without help for at least 10 seconds but could not stand or walk
- Could usually eat without feeding support
- Could usually breathe without help or with some help from a breathing machine

Babies born with SMA and **3 copies of the *SMN2* gene** can have symptoms start before they are 12 months of age.

Participants took part at 11 trial sites in the United States.

What treatments did the participants receive?

The treatment in this trial was:

AVXS-101, also known as **onasemnogene abeparvovec** (pronounced on-a-SEM-noe-jeen a-be-PAR-voe-vek), which was given one time as an intrathecal injection. Participants received 1 of 3 dose levels of AVXS-101:

- **Lower dose**, given to participants in the younger age group
- **Medium dose**, given to participants in both age groups
- **Higher dose**, given to participants in the younger age group

This was an open-label trial, which means that the parents and clinical trial team knew which dose of AVXS-101 the participants received.

What happened during this trial?

Up to 2 months before treatment

During screening

Trial doctors checked participants' health and genetic test results to make sure they could be in this trial.

32 participants took part in this trial.

1 injection

During treatment

The participants were assigned to get 1 of 3 dose levels of AVXS-101 as an intrathecal injection:

- Lower dose: 3 participants in the younger age group
- **Medium dose**:
  - 13 participants in the younger age group
  - 12 participants in the older age group
- **Higher dose**: 4 participants in the younger age group

For safety, doctors first gave the lower dose to a group of participants and checked for safety concerns. Then, they gave the medium dose to the next group of participants, and then the higher dose to the next group of participants.

After receiving the intrathecal injection, participants and their family stayed at the hospital for 2 days so trial doctors could closely check their health.

Up to 15 months after treatment

During follow-up

For 12 months, participants had many follow-up visits for trial doctors to check their health. Participants who received the higher dose had an extra visit at 15 months. The researchers checked participants' ability to stand up on their own, ability to move, and their health.

During the COVID-19 pandemic, some visits were done by phone.

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

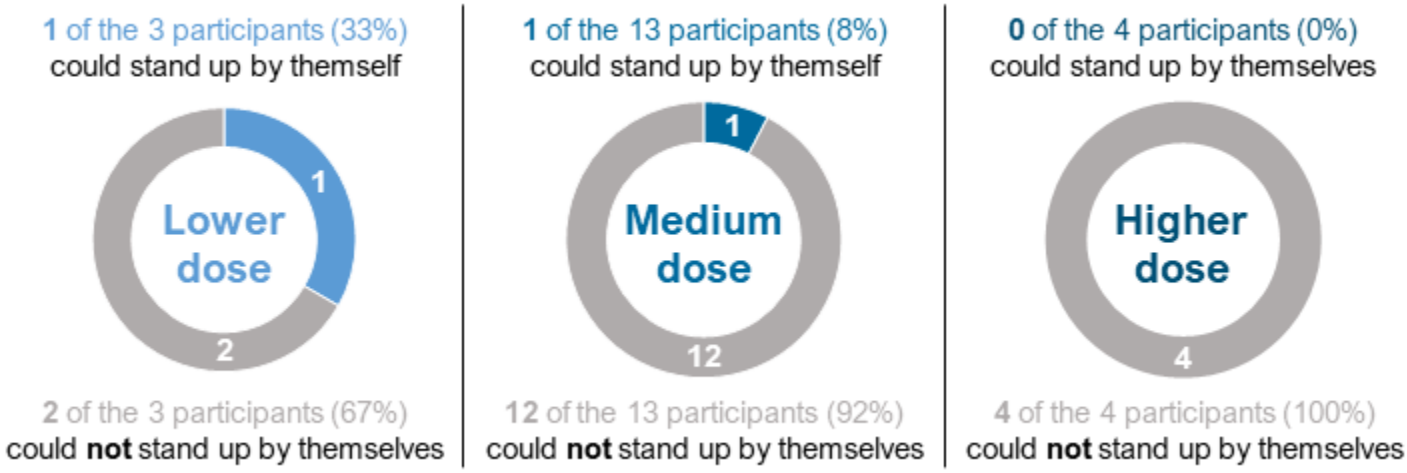
What were the main results of this trial?

How many of the participants in the younger age group could stand up without help for 3 seconds at least once by a year after treatment?

1 participant who received the lower dose (33%) and 1 who received the medium dose (8%) were able to stand up without help for 3 seconds by a year after treatment. No participants who received the higher dose could stand up.

To find this out, the trial staff took videos of the babies' ability to stand up at the trial visits. Each participant's parents could also take videos of the participant 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 2 years old.

The number of participants who were between ages 6 months and less than 2 years when they received AVXS-101 who could stand up by themselves



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

To learn if AVXS-101 had a meaningful effect on ability to stand up without help, the researchers compared the 13 participants in the younger age group who received the medium dose to 51 participants with SMA in a past observational study. The observational study was called the Pediatric Neuromuscular Clinical Research (PNCR) Network study. The lower and higher doses did not include enough participants to meaningfully compare with participants in the observational study.

In the PNCR study, 7 of the 51 participants (14%) could stand up without help for 3 seconds, compared to 1 out of 13 participants (8%) who received the medium dose of AVXS-101. The researchers concluded that, at the medium dose, AVXS-101 did not have a meaningful effect on the participants' ability to stand up without help for 3 seconds.

Could the participants in the older age group who received the medium dose move more by a year after treatment?

On average, the participants ages 2 to less than 5 years could move more by a year after receiving the medium dose. No participants in the older age group received the lower or higher doses.

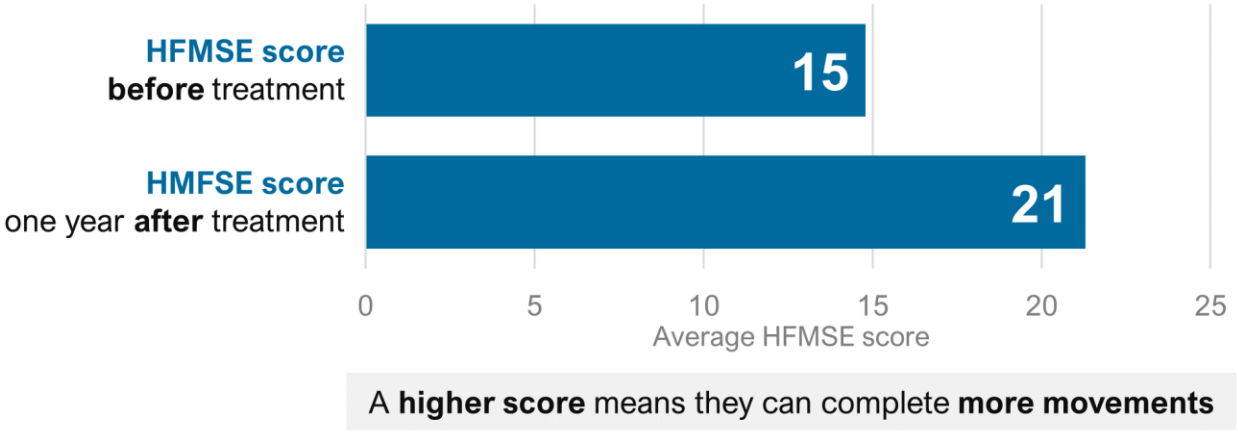
To find this out, the trial staff used the **Hammersmith Functional Motor Scale-Expanded (HFMSE)**. The HFMSE is a test that measures the ability of a child with SMA who is 2 years or older to do 33 movements including:

- Sitting up
- Rolling over
- Crawling
- Holding their head up
- Standing
- Stepping and walking

The score could range from 0 (not able to complete any movements in the HFMSE) to 66 (able to complete all movements in the HFMSE).

Researchers compared the HFMSE scores of the 12 participants in the older age group who received the medium dose from before treatment to a year after treatment. The average HFMSE score went up by about 6 points after treatment. A higher score means the participant can complete more movements.

Average HFMSE scores of participants who were between ages 2 to less than 5 years when they received the medium dose



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

To learn if AVXS-101 had a meaningful effect on ability to move, the researchers compared HMFSE scores of the 12 participants in the older age group who received the medium dose to 15 participants with SMA in the past PNCR observational study. The 15 participants in the PNCR study were similar to the participants in this trial but received standard of care because there were no treatments for SMA at the time.

In the PNCR observational study, the average HFMSE score went down from about 12 to 10 after a year. In this trial, the average HFMSE scores went up from about 15 points to about 21 points a year after treatment. The researchers concluded that the medium dose of AVXS-101 had a meaningful effect on ability to move for participants who received treatment between ages 2 and less than 5 years.

What medical problems did the participants 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 until a participant's last trial 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. 7 participants had serious adverse events. The most common serious adverse event, which happened in 2 participants, was:

- **A possible sign of liver or gallbladder damage** (Blood alkaline phosphatase increased)

Both participants who had this serious adverse event were in the younger age group. 1 received the lower dose and 1 received the medium dose.

What were the most common non-serious adverse events?

All 32 participants had adverse events that were not considered serious.

The table below shows the **non-serious adverse events** that happened in **7 or more** of **32** participants (more than about **20%**):

Age group:	Younger age group			Older age group
	Lower dose 3 participants	Medium dose 13 participants	Higher dose 4 participants	Medium dose 12 participants
Infection in the nose, throat, or airways Upper respiratory tract infection	2 of 3 67%	10 of 13 77%	3 of 4 75%	5 of 12 42%
Fever Pyrexia	3 of 3 100%	6 of 13 46%	2 of 4 50%	7 of 12 58%
Cough	0 of 3 0%	3 of 13 23%	1 of 4 25%	7 of 12 58%
Throwing up Vomiting	0 of 3 0%	5 of 13 39%	2 of 4 50%	3 of 12 25%
Constipation Trouble passing stool	0 of 3 0%	2 of 13 15%	2 of 4 50%	3 of 12 25%

How has this trial helped?

This trial helped researchers learn how well AVXS-101 works and if it is safe to give through an intrathecal injection to babies and children with SMA. The trial ended early because the sponsor decided they had collected enough information to answer their research questions.

The researchers found no new safety concerns for the participants in this trial. The safety results for the participants were similar to safety results from past trials where AVXS-101 was given as an IV infusion.

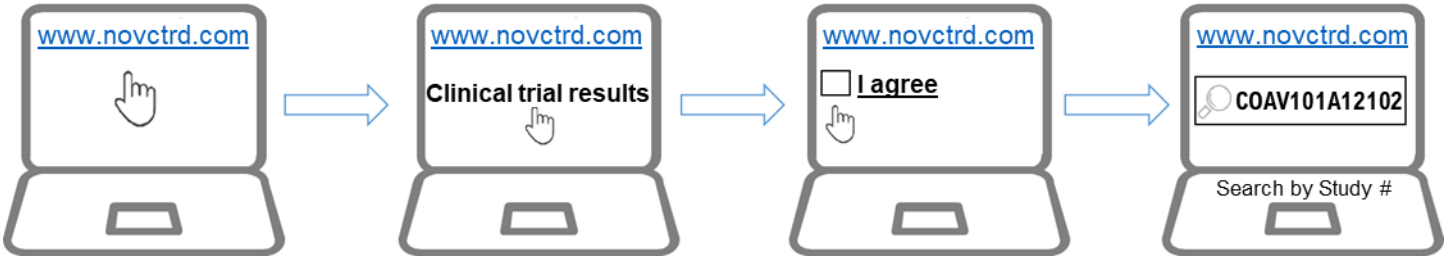
The researchers concluded that the medium dose of AVXS-101:

- Did not have a meaningful effect on the ability to stand up without help in participants in the younger age group (ages 6 months to less than 2 years when they received AVXS-101)
- Had a meaningful effect on the ability to move based on HFMSE scores in participants in the older age group (ages 2 to less than 5 years when they received AVXS-101)

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).

Follow these steps to find the scientific summary:



You can find more information about this trial on this website:

- www.clinicaltrials.gov. Use the NCT identifier **NCT03381729** in the search field.

Full clinical trial title: Phase 1, Open-Label, Dose Comparison Study of AVXS-101 for Sitting but Non-Ambulatory Patients with Spinal Muscular Atrophy

Thank you

Thank you to the children and their parents for taking part in this trial. As a clinical trial participant, your child 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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