Clinical Trial Results

NOVARTIS

Research Sponsor: Novartis
Drug Studied: LNA043
Protocol Number: CLNA043X2101

Thank you

Thank you to the participants who took part in the clinical trial for the trial drug LNA043. You and all of the participants helped researchers learn more about how LNA043 works and how safe it is to take.

Novartis sponsored this trial and believes it is important to share the results of the trial with you and the public. An independent non-profit organization called CISCRP prepared this summary of the trial results for you. We hope it helps you understand your important role in medical research.

If you participated in the trial and have questions about the results, please speak with the trial doctor or staff at your trial site.

What has happened since the trial ended?

The whole trial took over 2 years to finish. The amount of time each participant spent in the trial depended on which group they were in. The trial started in November 2015 and ended in March 2018.

The trial included 28 participants in the United States. After the trial ended, the sponsor reviewed the data and created a report of the results. This is a summary of that report.

Why was the research needed?

Before a trial drug can be approved for patients to take, researchers do clinical trials to find out how safe it is and how it works. This was the first time LNA043 was given to humans. Researchers are looking for a way to treat people with damage to their joint cartilage, like people with primary osteoarthritis.

Cartilage is a layer of firm, smooth tissue found between certain joints in the body, like the knee joint. The knee joint connects the upper leg bone to the lower shin bone. As people get older and put more stress on their bodies, this cartilage loses its smoothness. The 2 bones in the knee joint may start scratching against each other. This can stiffen the joint and make movement painful.

Cartilage is made up of cells called chondroblasts and chondrocytes. When cartilage gets damaged, the body helps to fix it by making new cells that can become chondroblasts and chondrocytes. But, the body is not always able to fix the damage on its own. The trial drug LNA043 is designed to act like a protein in the body that helps make more chondroblasts and chondrocytes. Researchers want to find out if LNA043 can help the body fix damaged cartilage.

In this trial, the researchers wanted to learn more about how safe LNA043 is to take. Researchers also wanted to find out if LNA043 got into the cartilage after being injected into the knee joint. The researchers compared LNA043 to a placebo. A placebo looks like the trial drug but does not have any medicine in it. Using a placebo helps researchers better understand the actual effect of a trial drug.

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

- What medical problems did the participants have?
- How else did treatment affect the participants' health?
- Did LNA043 move into the knee joint cartilage?
- How much LNA043 got into the blood?
- Did the participants have antibodies against LNA043?

To answer the questions in this trial, the researchers asked for the help of people with primary osteoarthritis who were scheduled to get a knee replacement. The men and women in the trial were 51 to 74 years old when they joined.

What kind of trial was this?

This trial was "double-blind". This means none of the participants, trial doctors, trial staff, or sponsor staff knew what treatment each participant got. In this trial, the participants got either LNA043 or the placebo.

Some trials are done this way because knowing what treatment the participants are getting can affect the results of the trial. When the trial ended, the sponsor found out which treatment each participant got so they could create a report of the results. The sponsor staff did not know the identity of any of the participants.

The researchers used a computer program to randomly choose the treatment each participant got. This helped make sure that comparing the results of the treatments was as fair as possible.

This was also a "dose-escalation" trial. This means that some of the participants took 1 treatment dose before the researchers increased the treatment dose for the rest of the participants. Researchers use dose-escalation trials to make sure a treatment dose is safe to take before they increase the dose given to other participants. The researchers carefully looked at the results of the participants who took the first treatment dose before deciding whether or not to give the next higher dose to the rest of the participants.

What happened during the trial?

Before the treatment started, the trial doctors did tests to make sure the participants could take part in the trial. This part happened for about 14 days before starting treatment. The trial doctors:

- checked the participants' overall health and asked what medicines they were taking
- asked the participants about any stiffness and pain in their knee, and how well they could do daily activities
- took blood and urine samples from the participants

The trial doctors also did these tests and took these samples during treatment and after treatment.

During treatment, the participants got LNA043 or the placebo 1 time through a needle put into their knee joint, also called an injection. Doses of LNA043 were measured in milligrams, also called mg.

The table below shows the 7 different treatment groups.

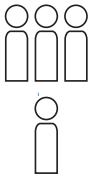
Group number	Treatment	Timing of treatment
Group 1	• 3 participants got 0.2 mg of LNA043 • 1 participant got the placebo	about 7 days before surgery
Group 2	• 3 participants got 2.0 mg of LNA043 • 1 participant got the placebo	about 7 days before surgery
Group 3	• 3 participants got 10.0 mg of LNA043 • 1 participant got the placebo	about 7 days before surgery
Group 4	• 3 participants got 20.0 mg of LNA043 • 1 participant got the placebo	about 7 days before surgery
Group 5	• 3 participants got 20.0 mg of LNA043 • 1 participant got the placebo	about 2 hours before surgery
Group 6	• 3 participants got 20.0 mg of LNA043 • 1 participant got the placebo	about 21 days before surgery
Group 7	• 3 participants got 40.0 mg of LNA043 • 1 participant got the placebo	about 7 days before surgery

Throughout the trial, the trial doctors took samples of the fluid in the participants' knee joints.

During each participant's knee replacement surgery, the trial doctors also took cartilage samples from the knee joint that was taken out.

After treatment ended, the participants had a final check-up about 28 days after their knee replacement surgery. During this visit, the trial doctors checked the participants' health and took blood and urine samples.

The chart below shows the treatments the participants got in this trial.

	• 21 participants got 0.2 mg to 40.0 mg LNA043. • 7 participants got the placebo.
	• The participants got LNA043 or the placebo through an injection into the knee joint.
	• The participants got LNA043 or the placebo 1 time, either 2 hours, 7 days, or 21 days before their knee replacement surgery.

What were the results of the trial?

This is a summary of the overall results of your trial, not your individual results. The results presented here are for a single trial. Other trials may provide new information or different results. You should not make medical decisions based on the results of a single trial. Always talk to a doctor before making any changes to your medications or treatment plans.

What medical problems did the participants have?

The researchers wanted to know what medical problems the participants had during the trial. They also wanted to know if the participants' health was affected in other ways during the trial, and how much knee pain they had after getting trial treatment.

Medical problems that happen in clinical trials are called "adverse events". An adverse event is any 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 drug. A lot of research is needed to know whether a drug causes a medical problem. During a trial, all medical problems are reported and written down, whether or not they are caused by the trial drug. So, when new drugs are being studied, researchers keep track of all medical problems that participants have.

How many participants had adverse events?

In this trial:

- 67.9% of the participants had adverse events. This was 19 of the 28 participants.
- 17.9% of the participants had serious adverse events during the trial. This was 5 of the 28 participants.

None of the participants stopped getting trial treatment because of an adverse event.

The tables below shows how many participants in each treatment group had adverse events during this trial.

How many participants had adverse events?

Group 1 0.2 mg LNA043 (Out of 3 participants)	Group 2 2.0 mg LNA043 (Out of 3 participants)	Group 3 10.0 mg LNA043 (Out of 3 participants)	Group 4 20.0 mg LNA043 (Out of 3 participants)	Group 5 20.0 mg LNA043 (Out of 3 participants)	Group 6 20.0 mg LNA043 (Out of 3 participants)	Group 7 40.0 mg LNA043 (Out of 3 participants)	Placebo (Out of 7 participants)
33.3% (1)	100.0% (3)	100.0% (3)	66.7% (2)	66.7% (2)	0.0% (0)	100.0% (3)	71.4% (5)

How many participants had serious adverse events?

Group 1 0.2 mg LNA043 (Out of 3 participants)	Group 2 2.0 mg LNA043 (Out of 3 participants)	Group 3 10.0 mg LNA043 (Out of 3 participants)	Group 4 20.0 mg LNA043 (Out of 3 participants)	Group 5 20.0 mg LNA043 (Out of 3 participants)	Group 6 20.0 mg LNA043 (Out of 3 participants)	Group 7 40.0 mg LNA043 (Out of 3 participants)	Placebo (Out of 7 participants)
0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	28.6% (2)

What were the most common serious adverse events?

In this trial, 5 participants had a total of 10 serious adverse events.

The serious adverse events below happened in the participants who got LNA043:

- Anemia, which is a condition of having low levels of healthy red blood cells
- Blood clot in a deep vein
- Blood clot in the lungs
- Bacterial skin infection after the surgery
- Swelling in the digestive tract
- Bacterial skin infection
- Dehydration

The serious adverse events below happened in the participants who got the placebo:

- Blood clot in the lungs
- Low blood pressure
- Breathing that stopped for some time

Researchers thought that some of these serious adverse events were considered typical for having total knee replacement surgery.

None of the participants died during this trial.

What were the most common adverse events?

The most common adverse event in this trial was constipation. This happened in 25.0% of the participants. This was 7 of the 28 participants.

The table below show the adverse events that happened in at least 10% of the participants in this trial. There were other adverse events, but these happened in fewer participants.

Most common adverse events in this trial

	Group 1 0.2 mg LNA043 (Out of 3 participants)	Group 2 2.0 mg LNA043 (Out of 3 participants)	Group 3 10.0 mg LNA043 (Out of 3 participants)	Group 4 20.0 mg LNA043 (Out of 3 participants)	Group 5 20.0 mg LNA043 (Out of 3 participants)	Group 6 20.0 mg LNA043 (Out of 3 participants)	Group 7 40.0 mg LNA043 (Out of 3 participants)	Placebo (Out of 7 participants)
Constipation	0.0% (0)	66.7% (2)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	42.9% (3)
Dizziness	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)
Anxiety	0.0% (0)	66.7% (2)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)
Nausea	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Low levels of healthy red blood cells	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)
Low blood pressure	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	14.3% (1)
Unable to sleep normally	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	14.3% (1)

How else did treatment affect the participants' health?

The researchers also wanted to know if LNA043 affected the participants' health in other ways, like:

- how much knee-related pain they had after getting the injection
- if the participants' blood and urine tests changed after getting the injection

Knee-related pain

To find out about the participants' knee-related pain, the researchers used a survey called the Knee Injury and Osteoarthritis Outcome Score, also known as KOOS. The trial doctors asked the participants to take this survey each day for 7 days after they got the injection of trial treatment. The participants answered questions about their knee pain, discomfort, and ability to do daily activities. The doctors gave them a score for each question. Higher scores meant fewer symptoms.

Overall, the researchers found that there were no differences between the treatment groups in how the participants felt about their knee pain and discomfort. This was true for the participants who got LNA043 and the participants who got the placebo.

Blood and urine health tests

To find out about the participants' blood and urine tests, the researchers compared the levels of different proteins and cells in the blood and urine. The researchers looked at these levels throughout the trial.

Overall, the researchers also found no differences between the treatment groups in the participants' blood and urine tests. Researchers did not think that any of the changes in these tests were related to treatment with LNA043 or the placebo.

Did LNA043 move into the knee joint cartilage?

Yes. To answer this question, the trial doctors looked at samples of the participants' knee joint cartilage that was taken out during surgery. They wanted to see if LNA043 could be found in the cartilage after LNA043 was injected into the knee joint.

Overall, the researchers found that:

- LNA043 was not found in the knee's cartilage in any treatment group except for Group 5.
- In Group 5, LNA043 was found to attach to cartilage in the knee, and then move quickly out of the knee joint.

How much LNA043 got into the blood?

The researchers wanted to know if LNA043 moved from the knee joint into the participants' bloodstream. To find out, the trial doctors tested the participants' blood at different times after they got the injection.

Overall, the researchers found that the participants who got the LNA043 knee injection had LNA043 in their blood within a few hours after getting the injection. But, LNA043 was gone from the bloodstream 3 days after getting treatment.

Did the participants have antibodies against LNA043?

No. The researchers wanted to know if the participants had antibodies against LNA043. Antibodies are normally made by the immune system to find anything the body does not recognize. This is how the body knows to fight infections by bacteria and viruses. Sometimes the immune system makes antibodies that bind to treatments. This can stop the treatment from working.

The researchers studied the participants' blood samples. They found that none of the participants in this trial had antibodies against LNA043.

How has this trial helped patients and researchers?

This was the first time LNA043 was given to humans. The information described above helped the researchers learn more about how safe LNA043 is to take, how much gets into the blood, and if it is found in the cartilage after injection into the knee. The results from many trials are needed to find out which treatments can be used for patients with damaged cartilage.

The results presented here are for a single trial. This summary shows only the main results from this one trial in a small number of participants with primary osteoarthritis. Other trials may provide new information or different results. It takes volunteers in many trials all around the world to advance medical science.

Where can I learn more about this trial?

More information about the results of this trial can be found in the scientific results summary available on the Novartis Clinical Trial Results website (www.novctrd.com). Once on the site, click **"READ MORE"** under **"Clinical trial results"** at the bottom of the page. After agreeing to enter the Novartis website, type **"CLNA043X2101"** into the keyword search box and click **"Search"**. If you have questions about the results, please speak with the trial doctor or staff at your trial site.

You can find more information about this trial on the websites listed below.

- www.clinicaltrials.gov. Once you are on the website, type **"NCT02491281"** into the search box and click **"Search"**.

If more clinical trials are planned, they will be listed on the above public websites or www.novartisclinicaltrials.com. Search for **"LNA043"**.

Full trial title: A randomized, placebo controlled, double-blind first in human single ascending dose study of LNA043 in primary osteoarthritis patients scheduled for total knee replacement

Thank you

As a clinical trial participant, you belong to a large community of participants around the world. You helped researchers answer important health questions and test new medical treatments.

CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation.

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