NOVARTIS

The safety and effects of LNA043 for people with damaged cartilage in the knee

Thank you!

Thank you to the participants who took part in the clinical trial for the trial drug **LNA043**. Every participant helped the researchers learn more about LNA043 for people with **damaged cartilage in the knee** or **knee osteoarthritis**.

Novartis sponsored this 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 participants understand their important role in medical research.

Trial information

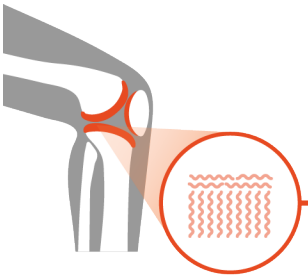
Trial number: CLNA043X2202
Drug studied: LNA043
Sponsor: Novartis

If you were a participant and 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 results.

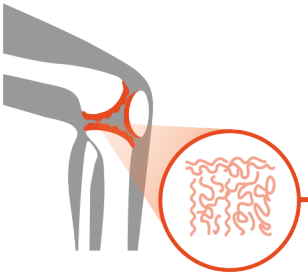
What was the main purpose of this trial?

The purpose of this trial was to help researchers learn more about the safety of LNA043. It was also designed to help researchers learn more about the effects of LNA043 for people with damaged cartilage in the knee or knee osteoarthritis.



Cartilage is the bendable tissue that covers the ends of bones so they don't rub together. It cushions the bones, like a shock absorber, and helps the knee move smoothly.

Healthy cartilage is structured with organized layers of smooth tissue.



Damaged cartilage in the knee means there are tears or holes in the cartilage that covers the ends of the knee bones. It is often caused by a knee injury.

When the body repairs **damaged cartilage**, the tissue can be less smooth and organized, like when a scar forms on skin.

The trial drug **LNA043** is a protein designed to help cartilage grow and heal.

The trial had 2 parts:

- **Part A** included participants with damaged cartilage in the knee. This part looked at the safety and effects of a low dose of LNA043.
- **Part B** included participants with knee osteoarthritis. This part looked at the safety and effects of a low and high dose of LNA043.

The main questions this trial was designed to answer:

- What adverse events did the participants have during this trial?
  An adverse event is any sign or symptom that participants have during a trial.
- Was there a change in how knee cartilage tissue was organized for participants in Part A?
- Was there a change in the amount and thickness of knee cartilage for participants in Part B?

How long was this trial?

The trial began in September 2017 and ended in September 2022. It was planned for the participants to be in the trial for 13 months in Part A and for 14 months in Part B. This included the health checks at the start of the trial to the last time the trial staff checked in with them. Participants started the trial on different dates.

Who was in this trial?

Participants joined either Part A or Part B:

Part A

58 participants with **damaged cartilage in the knee** – 32 men and 26 women. They were 22 to 55 years old.

Participants reported their race as:

- White (Caucasian) – 53 participants
- Asian – 2 participants
- American Indian or Alaska Native – 1 participant
- Black or African American – 1 participant
- Unknown – 1 participant

Part B

83 participants with **knee osteoarthritis** – 23 men and 60 women. They were 41 to 76 years old.

Participants reported their race as:

- White (Caucasian) – 70 participants
- Black or African American – 11 participants
- Asian – 1 participant
- Other – 1 participant

This trial took place in these countries:

- **Czech Republic** | 49 participants
- **Denmark** | 5 participants
- **The United States** | 87 participants

What trial treatments did the participants receive?

The participants received their assigned treatment as injections into one knee joint. A computer program was used to randomly assign the treatments. This helped make sure the researchers compared the results as fairly as possible.

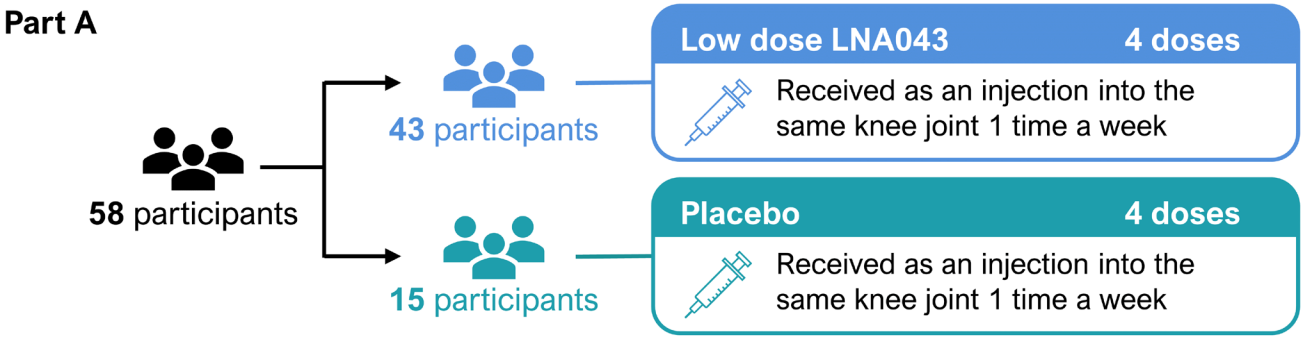
The participants, researchers, and trial staff did not know what treatment each participant received during the trial. Some trials are done this way because knowing what treatment participants receive can influence the results. Not knowing what treatment participants receive helps to make sure the results are looked at fairly.

Participants could not receive certain medicines for their knee condition during the trial, such as corticosteroids. They could take certain medicines for knee pain.

Part A trial treatments:
Participants in Part A were randomly assigned to one of these treatment groups:

- **Low dose LNA043** – 20 milligrams (mg)
- **Placebo** – looks like the trial drug but has no trial drug in it

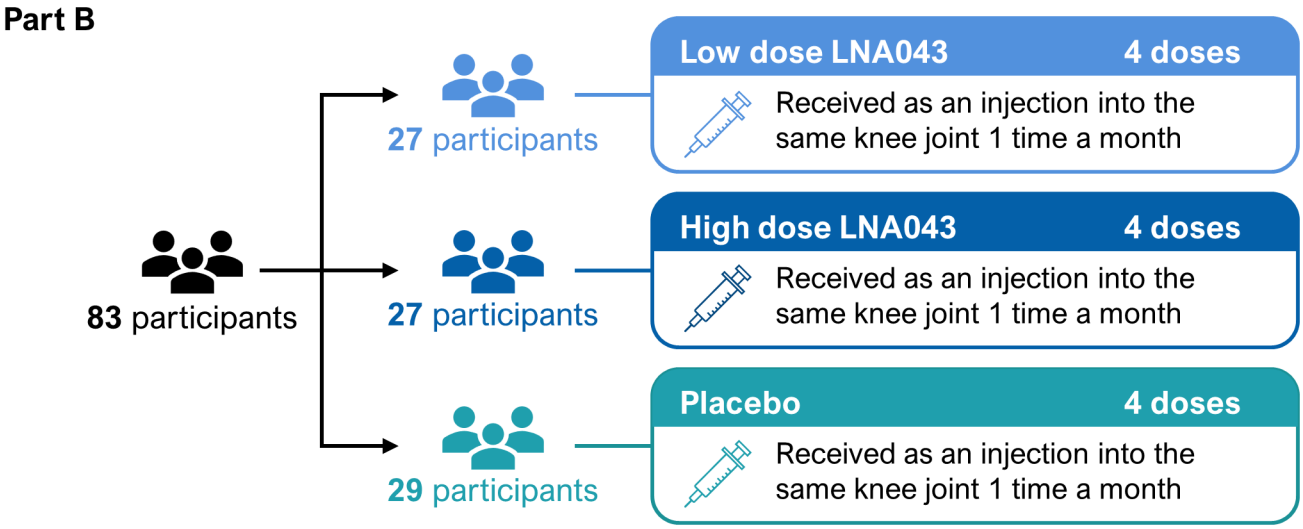
The graphic below shows how many doses and how often the different treatments were given in Part A.



Part B trial treatments:
Participants in part B were randomly assigned to one of these treatment groups:

- **Low dose LNA043** – 20 mg
- **High dose LNA043** – 40 mg
- **Placebo** – looks like the trial drug but has no trial drug in it

Based on earlier results, the researchers changed how often the treatment would be given in Part B. The graphic below shows how many doses and how often the treatment was given in Part B.



What were the main results of this trial?

What adverse events did the participants have during this trial?

Trial doctors keep track of **all** adverse events that happen in trials, even if they think the adverse events are **not** related to the trial treatments.

Many trials are needed to know if a drug or treatment causes an adverse event.

The adverse events in this section include any that happened during treatment and up to about 1 year after starting treatment.

An adverse event is:

- Any **sign or symptom** that the participants have during a trial
- Considered **serious** when it is life-threatening, causes lasting problems, the participant needs hospital care, or results in death

Adverse events **may** or **may not** be caused by treatments in the trial.

Part A:
During treatment, less than half of the participants (26 out of 58) had adverse events. None of the adverse events were considered serious.

After treatment, less than half of the participants (17 out of 58) had adverse events. 2 participants had an adverse event that was considered serious.

The most common adverse events were joint pain and headache.

Part B:
During treatment, less than half of the participants (31 out of 83) had adverse events. 1 participant had an adverse event that was considered serious.

After treatment, less than half of the participants (21 out of 83) had adverse events. 3 participants had one or more adverse events that were considered serious.

The most common adverse event was joint pain.

The researchers concluded there were no new safety concerns for LNA043 in this trial.

How many participants had adverse events?

Part A: The table below shows the number of participants who had adverse events.

Participants who:	**During** treatment		**After** treatment	
	Low dose LNA043 **43** participants	**Placebo** **15** participants	**Low dose LNA043** **43** participants	**Placebo** **15** participants
Had at least 1 **adverse event**	**44%** 19 of 43	**47%** 7 of 15	**37%** 16 of 43	**7%** 1 of 15
Had at least 1 **serious adverse event**	**0%** 0 of 43	**0%** 0 of 15	**5%** 2 of 43	**0%** 0 of 15
Left the trial due to an **adverse event**	**0%** 0 of 43	**0%** 0 of 15	**0%** 0 of 43	**0%** 0 of 15

Part B: The table below shows the number of participants who had adverse events.

Participants who:	During treatment			After treatment		
	Low dose LNA043 27 participants	High dose LNA043 27 participants	Placebo 29 participants	Low dose LNA043 27 participants	High dose LNA043 27 participants	Placebo 29 participants
Had at least 1 **adverse event**	22% 6 of 27	56% 15 of 27	34% 10 of 29	11% 3 of 27	19% 5 of 27	41% 12 of 29
Had at least 1 **serious adverse event**	4% 1 of 27	0% 0 of 27	0% 0 of 29	4% 1 of 27	0% 0 of 27	7% 2 of 29
Left the trial due to an **adverse event**	0% 0 of 27	0% 0 of 27	0% 0 of 29	0% 0 of 27	0% 0 of 27	0% 0 of 29

What were the serious adverse events?

In Part A:
2 participants who received the **low dose of LNA043** had a serious adverse event **after treatment.**
These were:

- **Back pain**
- **Fluid-filled sac in the jawbone** | odontogenic cyst

In Part B:
1 participant who received the **low dose of LNA043** had a serious adverse event **during treatment**.
This was:

- **Lung infection caused by COVID-19 leading to a hospital stay** | COVID-19 pneumonia

1 participant who received the **low dose of LNA043** had a serious adverse event **after treatment**.
This was:

- **Cancer of blood and bone marrow** | Acute myeloid leukemia

2 participants who received the **placebo** had serious adverse events **after treatment**.
These were:

- **Blood clot in a major vein** | Vena cava thrombosis
- **Blood clot in a vein** | Deep vein thrombosis
- **Low level of red blood cells due to blood loss** | Blood loss anemia
- **Swelling of the colon due to a lack of blood** | Colitis ischemic

No participants died during either Part of the trial.

What were the other adverse events?

In Part A: The table below shows the adverse events that happened in **4 or more participants**. Additional adverse events happened in fewer participants.

	During treatment		**After** treatment	
	Low dose LNA043 43 participants	**Placebo** 15 participants	**Low dose LNA043** 43 participants	**Placebo** 15 participants
Joint pain Arthralgia	7% 3 of 43	7% 1 of 15	7% 3 of 43	0% 0 of 15
Headache	14% 6 of 43	7% 1 of 15	0% 0 of 43	0% 0 of 15
Infection in the nose, throat and airways Upper respiratory tract infection	2% 1 of 43	7% 1 of 15	5% 2 of 43	7% 1 of 15
Back pain	2% 1 of 43	7% 1 of 15	2% 1 of 43	7% 1 of 15
Joint swelling	9% 4 of 43	0% 0 of 15	0% 0 of 43	0% 0 of 15

In Part B: The table below shows the adverse events that happened in **5 or more participants**. Additional adverse events happened in fewer participants.

	During treatment			**After** treatment		
	Low dose LNA043 27 participants	**High dose LNA043** 27 participants	**Placebo** 29 participants	**Low dose LNA043** 27 participants	**High dose LNA043** 27 participants	**Placebo** 29 participants
A possible sign of muscle damage Blood creatinine phosphokinase increased	4% 1 of 27	4% 1 of 27	0% 0 of 29	0% 0 of 27	4% 1 of 27	7% 2 of 29
Joint swelling	4% 1 of 27	4% 1 of 27	10% 3 of 29	0% 0 of 27	0% 0 of 27	0% 0 of 29
Joint pain Arthralgia	4% 1 of 27	15% 4 of 27	3% 1 of 29	0% 0 of 27	7% 2 of 27	7% 2 of 29

Part A results

Was there a change in how the participants' knee cartilage tissue was organized?

The researchers concluded there was no clear change in how the knee cartilage tissue was organized at 7 months after starting treatment. This was found for the participants who received either the low dose of LNA043 or the placebo.

The trial staff took images of each participant's knee using magnetic resonance imaging, also known as MRI. The researchers compared MRI images of different cartilage layers to measure the change in how participants' knee cartilage tissue was organized. They compared the MRI results from before treatment to up to 7 months after starting treatment. A higher MRI result means the cartilage structure is less organized.

Average change in how the participants' overall knee cartilage tissue was organized

Low dose LNA043
The MRI result of participants' knee cartilage tissue **was 6 units higher** 7 months after starting treatment.

Placebo
The MRI result of participants' knee cartilage tissue **was 2 units higher** 7 months after starting treatment.

The researchers concluded there was **no clear change** in the organization of the knee cartilage tissue in either group.

These results only include participants who completed their assigned treatment and had MRI images of their cartilage measured.

What other results were learned in Part A?

Did participants have signs of knee cartilage growth?

The researchers concluded participants who received LNA043 had slightly more signs of knee cartilage growth compared to placebo. This was found at 4 and 7 months after starting treatment.

The researchers only saw this difference in cartilage growth in certain damaged areas of the knee joint. Other damaged areas had no change in cartilage growth. No growth was seen in areas with healthy cartilage.

To learn this, the researchers used MRI images of the knee to measure the signs of cartilage growth in the participants' knee joint. The researchers looked at the end of the thigh bone and the kneecap, which are part of the knee joint. They found signs of more cartilage growth at the end of the thigh bone, but not behind the kneecap.

Based on the cartilage growth results, the researchers decided to continue with Part B.

Part B results

In Part B, not all MRI images collected were able to be measured due to poor image quality. The results below only include the images which could be measured. Because of this, there are fewer participants included in the results than planned. More research is needed to confirm these results.

Was there a change in the amount and thickness of participants' knee cartilage?

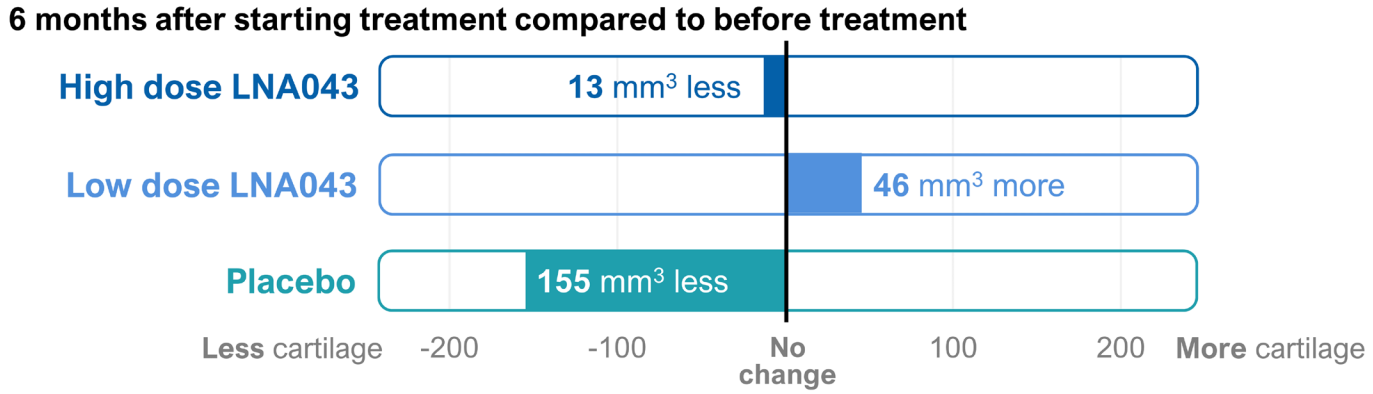
The participants who received the low dose of LNA043 tended to have a higher amount of cartilage in their knee compared to those who received the placebo. This was found 6 and 12 months after starting treatment.

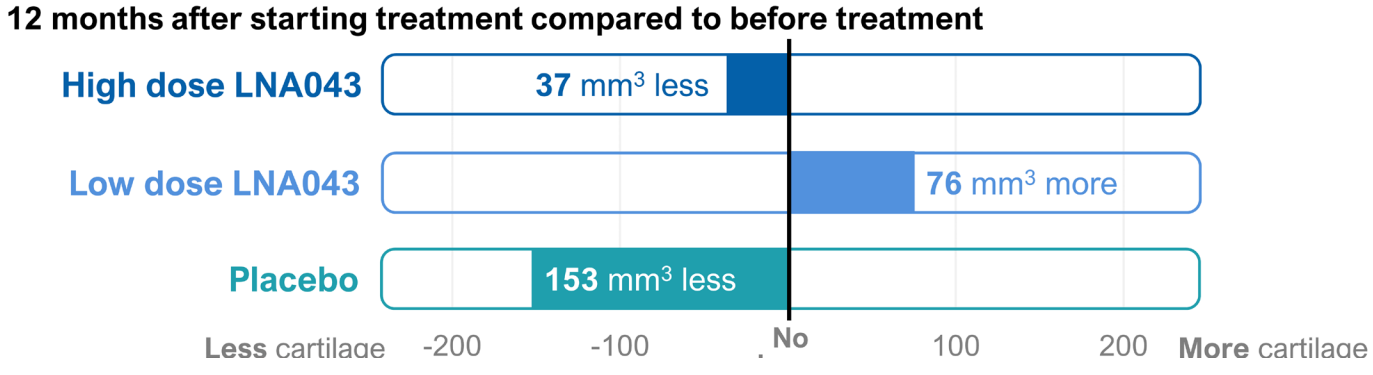
There was no clear difference in the thickness of knee cartilage for participants who received either dose of LNA043 compared to those who received the placebo after treatment.

To learn this, researchers looked for changes in the amount and thickness of the participants' knee cartilage using MRI images. They compared these measures from before treatment to 6 and 12 months after starting treatment.

Average change in the amount of participants' knee cartilage

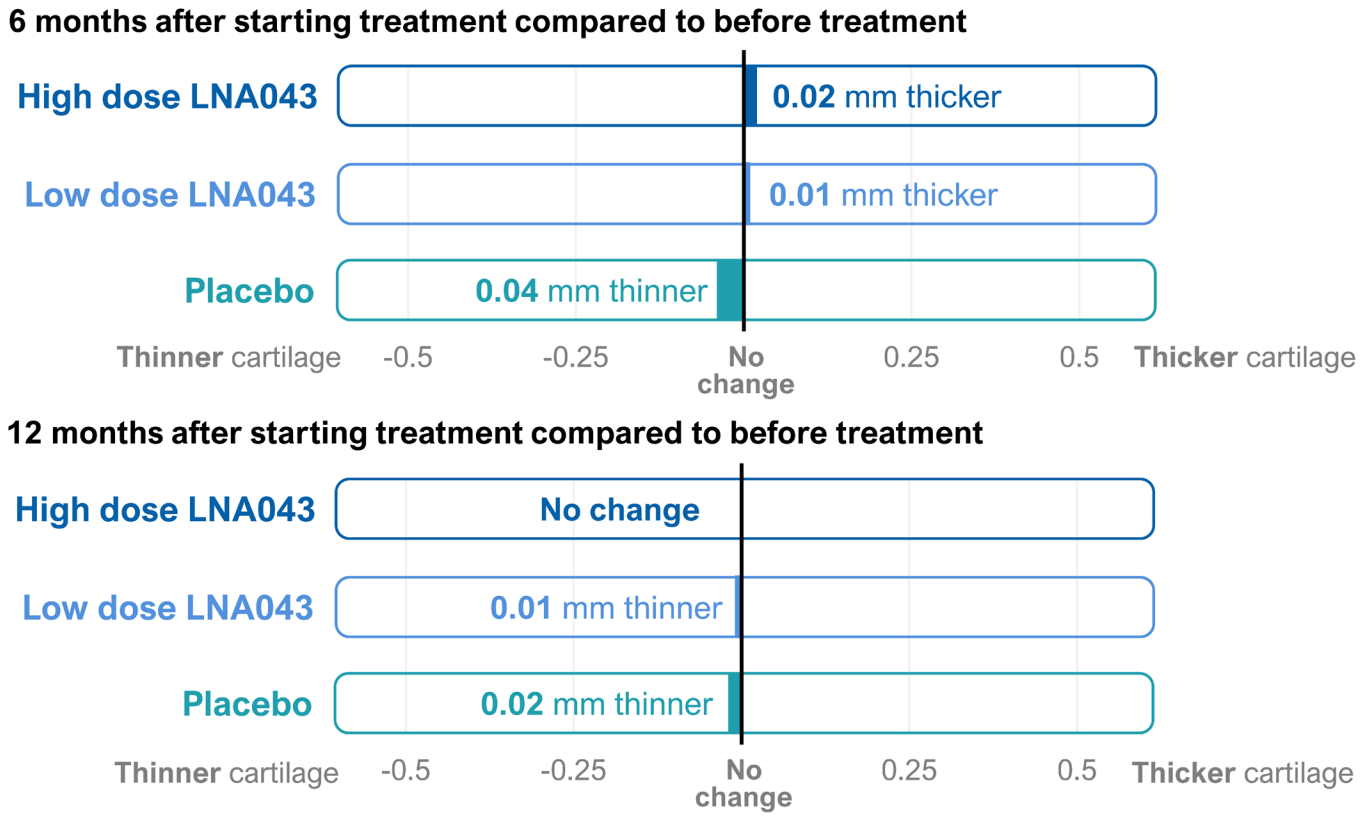
These charts show the average change in the amount of knee cartilage participants had 6 and 12 months after starting treatment. This measure combines the knee cartilage length, width, and height in cubic millimeters (mm^3).





Change in the thickness of participants' knee cartilage

This chart shows the average change in the thickness of cartilage participants had 6 and 12 months after starting treatment. The change in thickness was measured in millimeters (mm).



What other results were learned in Part B?

Was there a change in how the participants' knee cartilage tissue was organized?

There was no clear difference in how the knee cartilage tissue was organized up to 12 months after starting treatment. This was found for participants who received either dose of LNA043 compared to those who received the placebo.

To learn this, the researchers looked at how the tissue was organized in the participants' knee cartilage using MRI images.

What was learned from this trial?

This trial helped researchers learn about the safety and effects of LNA043 in people with damaged cartilage in the knee or knee osteoarthritis.

The researchers found no new safety concerns for LNA043 in this trial.

In Part A, the researchers concluded that in participants with damaged cartilage in the knee, overall:

- There was no clear change in how the knee cartilage tissue was organized in participants who received LNA043 compared to those who received the placebo
- The participants who received LNA043 had slightly more signs of knee cartilage growth compared to those who received the placebo

In Part B, not all MRI images collected were able to be measured due to poor image quality. Because of this, there were only a small number of participants who had MRI images with high quality. The researchers concluded that in this small number of participants with knee osteoarthritis, overall:

- The participants who received the low dose of LNA043 tended to have a higher amount of cartilage in their knee compared to those who received the placebo
- There was no clear difference in the thickness of knee cartilage for participants who received either dose of LNA043 compared to those who received the placebo after treatment
- There was no clear difference in how the knee cartilage tissue was organized in participants who received either dose of LNA043 compared to those who received the placebo

This was one of many trials a drug goes through. Other trials may have different results. This type of trial helped researchers learn about the safety and effects of a trial drug in a small number of participants.

Where can I learn more about this and future trials?

For more information about this trial go to any of the following websites:

- **novctrd.com** – search using the study number **CLNA043X2202**
- **clinicaltrials.gov** – search using the number **NCT03275064**
- **clinicaltrialsregister.eu/ctr-search** – search using the number **2016-004052-30**

At the time this summary was written, future trials are planned for LNA043 in damaged cartilage in the knee. Additional trials will appear on the public websites above. When there, search for **LNA043**, **articular cartilage lesions of the knee**, or **knee osteoarthritis**.

Full trial title:

A two-part randomized, placebo-controlled, patient and investigator blinded, study investigating the safety, tolerability and preliminary efficacy of intra-articular LNA043 injections in regenerating the articular cartilage of the knee in patients with articular cartilage lesions (Part A) and in patients with knee osteoarthritis (Part B)

If you participated in the trial and have **questions** about the results, please speak with the trial doctors or staff at your trial site. Always talk to a doctor before making any changes to your health care.

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