NOVARTIS

Clinical Trial Results Summary

A trial to learn more about how well the trial treatment inclisiran works and how safe it is in participants with a genetic condition of too much cholesterol in the bloodstream, called homozygous familial hypercholesterolemia

Trial Number: MDCO-PCS-17-02 or CKJX839A12302

Thank you

Thank you to the participants who took part in the clinical trial for inclisiran, also called KJX839. All of the participants helped the researchers learn about how well inclisiran works and how safe it is.

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.

If you participated in the trial and 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 on the last page of this summary.

What was the purpose of the trial?

In this trial, researchers are looking for a better way to treat people with homozygous familial hypercholesterolemia, also called “HoFH”.

What is HoFH?

HoFH is a rare genetic condition that is passed down through families. People may develop HoFH when they are “homozygous” for a specific gene. Homozygous means that a person has 2 identical copies of a specific “gene”. A gene is part of a person’s genetic makeup that gives instructions for the body to grow and work. In people with HoFH, the body does not remove enough of a type of cholesterol called “LDL-C” from the body.

Cholesterol is a fatty substance found naturally in the blood that is important for the body to function normally. But, too much cholesterol can cause health problems such as heart attacks and strokes.

LDL-C is a type of cholesterol that is sometimes called “bad” cholesterol. This is because it can build up in the walls of blood vessels and cause medical problems. In people with HoFH, the levels of LDL-C in the blood are often much higher than normal at an early age.

There are treatments available for doctors to give to people who have HoFH. However, patients sometimes need many different types of treatments, as the treatments they receive often do not reduce the levels of LDL-C in the blood well enough.

So, researchers are looking for a better way to treat patients with HoFH by lowering the levels of LDL-C in the blood.

Inclisiran was approved in the EU (December 2020) and US (Dec 2021) for use in adults with heterozygous familial hypercholesterolemia (HeFH).

In this trial, the researchers wanted to learn more about how well inclisiran works compared to a placebo and how safe inclisiran is in participants with HoFH.

A placebo looks like the trial treatment but has no trial treatment in it. Using a placebo helps researchers better understand the actual effects of a trial treatment.

How do researchers think the trial treatment can help?

The trial treatment, inclisiran, is designed to work by helping to reduce the levels of LDL-C in the blood.

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

- Did inclisiran help to reduce the amount of LDL-C in the participants' blood 150 days after starting treatment?
- What medical problems happened during this trial?

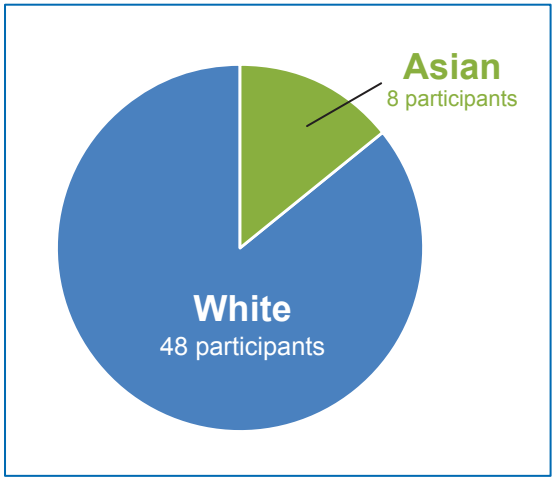
Who was in this trial?

To answer the questions in this trial, the researchers asked for the help of males and females who had HoFH. There were 56 participants in this trial.

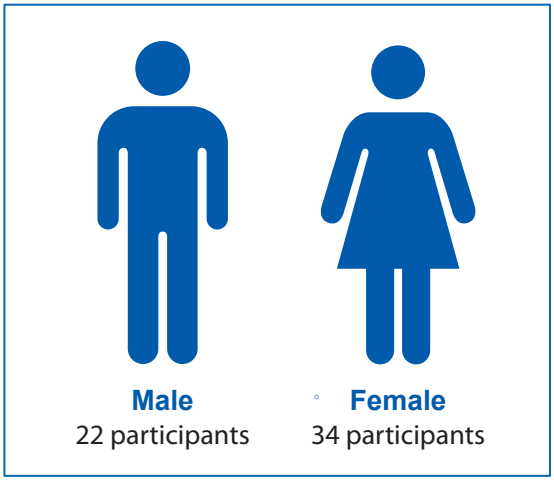
Everyone in this trial was between 22 and 70 years old when they joined the trial.

The charts below show the race and sex of the participants in this trial:

Participants' race (out of 56 participants)

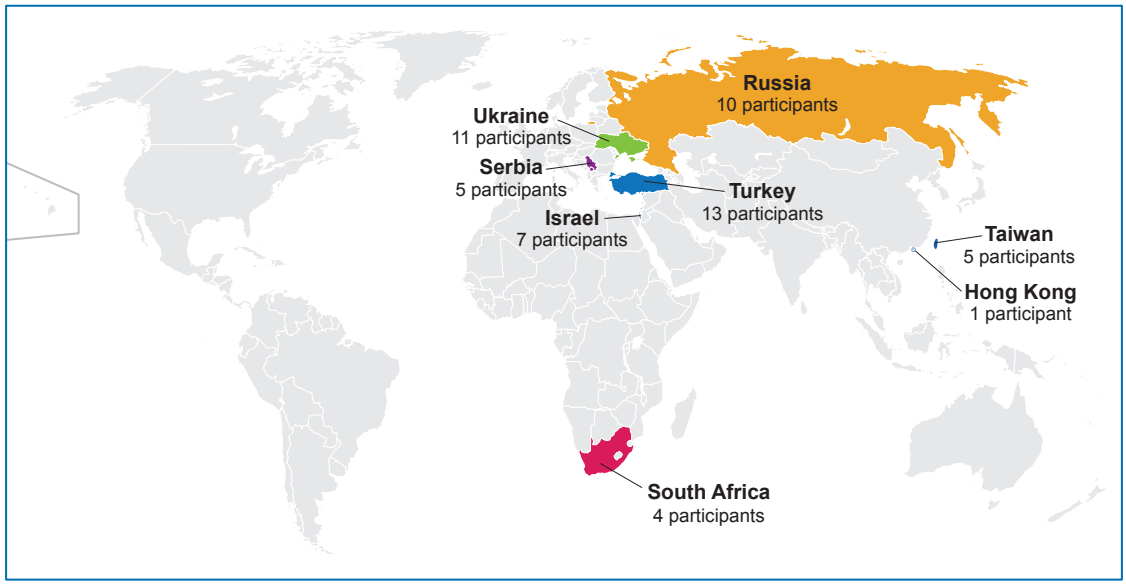


Participants' sex (out of 56 participants)



This trial included participants in Hong Kong, Israel, Russia, Serbia, South Africa, Taiwan, Turkey, and Ukraine.

Participants' countries (out of 56 participants)



What treatments did the participants receive?

The participants in this trial received either inclisiran or placebo as an injection under the skin. The doses of inclisiran were measured in milligrams, also called “mg”.

This trial had 2 parts: Part 1 and Part 2.

In Part 1:

- The participants received either **inclisiran** or **placebo** 2 times over a period of about 6 months.

In Part 1, the researchers used a computer program to randomly assign the treatment each participant received. This helped make sure the treatments were chosen fairly and comparing the results of the treatments was as accurate as possible.

Part 1 was the “double-blind” part of the trial. This means none of the participants, trial staff, or sponsor staff knew what trial treatment (inclisiran or placebo) each participant received.

After finishing Part 1, all but 3 of the participants continued into Part 2 of the trial.

In Part 2:

- All of the participants received **inclisiran** 3 or 4 times over a period of about 18 months. The participants who received inclisiran during Part 1 received inclisiran 3 times during Part 2. The participants who received placebo during Part 1 received inclisiran 4 times during Part 2.

Part 2 of this trial was the “open-label” part of the trial. This means the participants, researchers, trial doctors, and other trial staff knew that each participant received inclisiran in this part of the trial.

The chart below shows the treatments that the participants received during the trial.

	Part 1	Part 2
	inclisiran **or** placebo	inclisiran
	As an injection under the skin	
	2 times over a period of about 6 months	3 or 4 times over a period of about 18 months
	56 participants	53 participants

What happened during this trial?

The trial started in February 2019 and ended in September 2021. The participants were in the trial for about 2 years.

The chart below shows what happened during **Part 1** of this trial.

Before the participants received treatment

The trial doctors checked the participants' health and medical history to make sure they could be in the trial.

Up to 28 days

While the participants received treatment

The participants:

- Had their overall health checked.
- Had blood and urine samples taken.
- Answered questions about any medical problems they were having.
- Received their assigned treatment.

About 6 months

After the participants received their last treatment

- The participants visited their trial site.
- The doctors asked them questions about any medical problems they were having.
- The doctors checked the participants' overall health.

About 60 days after their last treatment in Part 1

The chart below shows what happened during **Part 2** of this trial.

Before the participants received treatment in Part 2

The trial doctors checked the participants' health. Then, they assigned the participants their treatment schedule depending on whether they received inclisiran or the placebo during Part 1.

About 90 days after their last treatment in Part 1

While the participants received treatment

The participants:

- Had their overall health checked.
- Had blood and urine samples taken.
- Answered questions about any medical problems they were having.
- Received their assigned treatment.

About 18 months

After the participants received their last treatment

- The participants visited their trial site.
- The doctors asked them questions about any medical problems they were having.
- The doctors checked the participants' overall health.

About 90 days after their last treatment in Part 2

What were the main results of this trial?

This is a summary of the overall results from this trial. The individual results of each participant might be different and are not in this summary.

The results from several trials are needed to decide which treatments are safest and work best. Other trials may provide new information or different results.

Did inclisiran help to reduce the amount of LDL-C in the participants' blood 150 days after starting treatment?

No. Overall, the researchers found that inclisiran did not help to reduce the amount of LDL-C in the participants' blood 150 days after starting treatment in **Part 1**.

The difference between the results of the treatments in this small study was too small for the researchers to know if inclisiran helped to reduce the amount of LDL-C in the participants' blood more than placebo.

To answer this question, the researchers:

- took blood samples from the participants before they received treatment, and at different times after they started treatment.
- measured the average change in the amount of LDL-C in the participants' blood from before they received treatment to 150 days after starting treatment.
- compared these results between the participants who received inclisiran and the participants who received placebo.

Overall, the researchers found that the average change in the amount of LDL-C in the participants' blood from before they received treatment to 150 days after starting treatment in **Part 1** was:

- **0.70% increase** in the participants who received **inclisiran**
- **2.39% increase** in the participants who received **placebo**

What medical problems happened during this trial?

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, results in death, causes lasting problems, or the participant needs hospital care.

An adverse event is an unwanted sign, symptom, or disease 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.

Adverse events may or may not be caused by the treatments in the trial. A lot of research is needed to know whether a treatment causes an adverse event. Doctors keep track of all the adverse events that happen in trials, even if they do not think the adverse events might be related to the treatments.

This section is a summary of the adverse events that happened during this trial.

How many participants had adverse events during Part 1?

The adverse events that happened in the 2 treatment groups during Part 1 of the trial are listed in the table below.

	Inclisiran (out of 37 participants)	**Placebo** (out of 19 participants)
At least 1 adverse event	**13 (35.1%)**	**6 (31.6%)**
At least 1 serious adverse event	**2 (5.4%)**	**1 (5.3%)**
Stopped treatment due to an adverse event	**0 (0.0%)**	**0 (0.0%)**
Deaths	**0 (0.0%)**	**0 (0.0%)**

How many participants had adverse events during Part 2?

The adverse events that happened during Part 2 of the trial are listed in the table below.

	Inclisiran (out of 53 participants)
At least 1 adverse event	**30 (56.6%)**
At least 1 serious adverse event	**11 (20.8%)**
Stopped treatment due to an adverse event	**0 (0.0%)**
Deaths	**3 (5.7%)**

What were the serious adverse events?

The table below shows all of the serious adverse events that happened during **Part 1**.

Serious adverse events during Part 1		
	Inclisiran (out of 37 participants)	**Placebo** (out of 19 participants)
Cancer of the digestive tract	**1 (2.7%)**	**0 (0.0%)**
Chest pain not related to the heart	**1 (2.7%)**	**0 (0.0%)**
Inflammation of the inner lining of the heart	**1 (2.7%)**	**0 (0.0%)**
Family stress	**0 (0.0%)**	**1 (5.3%)**

None of the participants died due to serious adverse events during **Part 1**.

The table below shows the serious adverse events that happened in more than 1 participant during **Part 2**. There were other serious adverse events, but each of those happened in only 1 participant.

Most common serious adverse events during Part 2	
	Inclisiran (out of 53 participants)
Lung infection caused by a virus	**2 (3.8%)**
Narrowing of a blood vessel near the heart	**2 (3.8%)**

There were 3 out of 53 participants (5.7%) who died due to serious adverse events during **Part 2**. These serious adverse events were:

- Lung infection caused by a virus
- More than 1 organ in the body failing to work
- Sudden death caused by loss of heart function

What were the most common adverse events?

The table below shows the adverse events that happened in more than 1 participant during **Part 1**. There were other adverse events, but each of those happened in only 1 participant.

Most common adverse events during Part 1		
	Inclisiran (out of 37 participants)	**Placebo** (out of 19 participants)
Infection in the nose, throat, and airways caused by a virus	**2 (5.4%)**	**2 (10.5%)**
Diarrhea	**2 (5.4%)**	**0 (0.0%)**
Fever	**2 (5.4%)**	**0 (0.0%)**
A condition in which the blood does not have enough healthy red blood cells	**1 (2.7%)**	**1 (5.3%)**
Swelling of the tonsils	**1 (2.7%)**	**1 (5.3%)**

The table below shows the adverse events that happened in 3 or more participants during **Part 2**. There were other adverse events, but those happened in fewer than 3 participants.

Most common adverse events during Part 2	
	Inclisiran (out of 53 participants)
Coronavirus infection	**4 (7.5%)**
Increased score on a test that measures the body's ability to stop bleeding as well as it should	**3 (5.7%)**

What was learned from this trial?

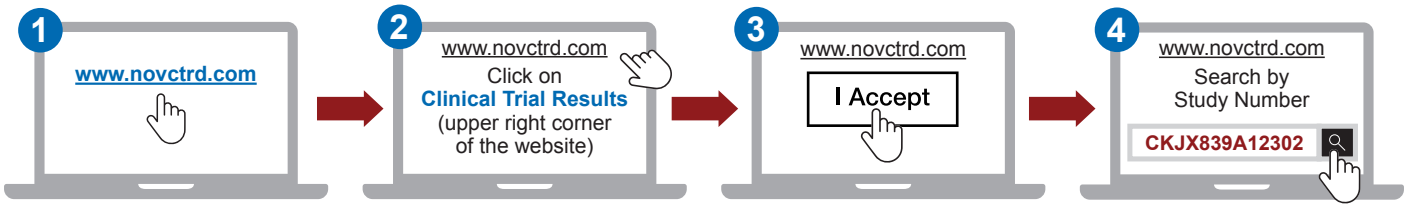
This trial helped the researchers to better understand if inclisiran can be a treatment option in participants with HoFH. However, this small study alone did not provide meaningful results. Further research might be necessary to learn more about whether inclisiran can help people with HoFH.

The results presented here are for a single trial. This summary shows only the main results from this one trial. If you have any questions, please talk to the doctor or staff at your trial site.

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.

Please follow the below steps:



You can find more information about this trial on the following websites:

- https://www.clinicaltrials.gov/. Use the NCT identifier NCT03851705 in the search field.
- www.clinicaltrialsregister.eu. Use the EudraCT identifier 2018-000893-31 in the search field.

Full trial title: A two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in subjects with homozygous familial hypercholesterolemia (HoFH) (ORION-5)

Protocol number: CKJX839A12302

ClinicalTrials.gov number: NCT03851705

EudraCT number: 2018-000893-31

Thank you

Clinical trial participants belong to a large community of participants around the world. They help researchers answer important health questions and study new medical treatments.

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