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Longterm safety and effectiveness of evinacumab in people with homozygous familial hypercholesterolemia a plain language summary

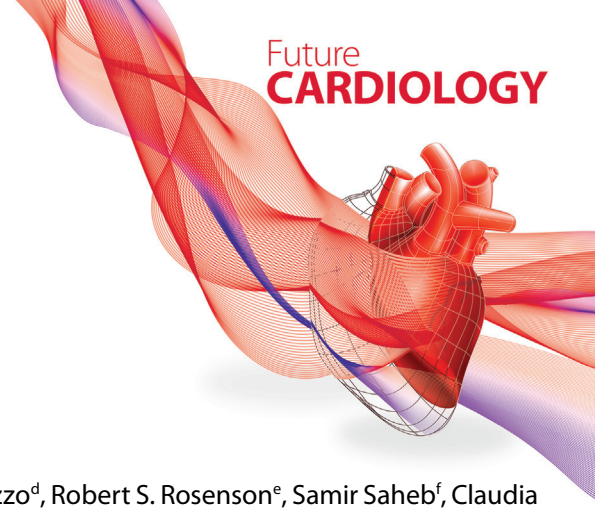
D Gaudet; S Greber-Platzer; L Reeskamp; G Iannuzzo; E et al ...

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Plain Language Summary of Publication

Future CARDIOLOGY



Long-term safety and effectiveness of evinacumab in people with homozygous familial hypercholesterolemia: a plain language summary

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Where can I find the original article on which this summary is based?

The original article is called 'Evinacumab in homozygous familial hypercholesterolaemia: long-term safety and efficacy' and has been published in the *European Heart Journal*. You can read it for free at: https://academic.oup.com/eurheartj/article/45/27/2422/7689553

Summary

What is this summary about?

This summary explains the results of a study looking at the long-term effects of a treatment called evinacumab. This study included people aged over 12 years with homozygous familial hypercholesterolemia, also known as HoFH. HoFH is a rare **genetic disorder** that makes the liver less able to remove excess 'bad' **cholesterol** (called **low-density lipoprotein cholesterol**, or LDL-C) from the body. LDL-C is considered 'bad' cholesterol because it increases the risk of heart disease and stroke. High levels of LDL-C increase the risk of developing serious heart problems early in life. Treatment options for lowering LDL-C often do not work very well for people with HoFH. Evinacumab is a medicine that is approved for the treatment of HoFH as an add-on to other therapies that lower LDL-C. The effect of evinacumab on heart problems such as heart attacks, stroke, or death is not known. In the UK, evinacumab is approved for people with HoFH aged 6 months and above. In Canada and the USA, evinacumab is approved for people with HoFH aged 5 years and above. In the European Union/European Economic Area, evinacumab is approved for people with HoFH aged 6 months and above. In Japan, evinacumab is approved for all ages of people with HoFH. More recently, evinacumab has also been approved in Brazil and Israel.

How to say (download PDF and double click sound icon to play sound)...

- **Angiopoietin-like-3:** AN-jee-o-po-EET-in like three
- **Atherosclerosis:** ATH-er-o-scler-O-sis
- **Cholesterol:** kol-EST-er-ol
- **Corneal arcus:** KORN-e-al ARK-us
- **Evinacumab:** EH-vin-A-cue-mab
- **Homozygous familial hypercholesterolemia:** HO-mo-ZI-gus fam-IL-i-al HY-per-kol-EST-er-ol-e-me-a
- **Tendon xanthomas:** TEN-don ZAN-tho-MAS
- **Xanthelasmas:** ZAN-the-LAS-mas

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What were the results?

People with HoFH who took part in the study were treated with evinacumab every 4 weeks for up to 44 months.

After 6 months of treatment, LDL-C levels were almost 44% lower than when people started the study.

Treatment-emergent adverse events, also called **TEAEs**, were reported by 80% of people in the study but most of these were mild (23.3%) or moderate (41.4%) in severity. The most commonly reported **side effects** which happened during the study were common cold, COVID-19, headache, flu-like illness, general pain, back pain, nausea, and cough. The study researchers determined that most of these reported side effects (91%) were not related to the use of evinacumab.

No serious TEAEs were considered related to evinacumab treatment. Nearly all of the people (97%) could continue with the study treatment and, based on this, the researchers concluded that evinacumab was generally well tolerated.

Genetic disorder: A condition caused by a change in one or more genes.
Cholesterol: A type of fat in the blood made by the liver and found in some foods. There are two main types of cholesterol: high-density lipoprotein cholesterol (HDL-C, also called 'good' cholesterol because it helps remove excess cholesterol from the body and can lower the risk of heart disease and stroke) and low-density lipoprotein cholesterol (LDL-C, also called 'bad' cholesterol).
Low-density lipoprotein cholesterol (LDL-C): A type of cholesterol found in the blood, which is needed to transport fat molecules to cells. It is sometimes called 'bad' cholesterol because too much LDL-C can cause heart problems and strokes.
Lipoprotein: A substance that is made up of both lipid (fat) and protein; it transports cholesterol around the body in the blood.
TEAEs: Treatment-emergent adverse events are medical problems that are reported by people in the study while they are receiving treatment. The medical problems may or may not be caused by the study treatment (evinacumab in this case).
Side effects: Any condition that deviates from a state of normal health, it can include illnesses, injuries, diseases, disorders, or any impairment that need medical treatment.

What do the results mean?

This study showed that evinacumab lowered 'bad' cholesterol in people with HoFH, and that this result lasted for a long period of time.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all the available evidence not on the results of a single study.

Who is this article for?

This article may be helpful for people with HoFH, or their families and caregivers. People who treat those with HoFH or want to learn more about the disease may also find it useful.

Who sponsored this study?

The study was **sponsored** by Regeneron Pharmaceuticals, Inc.

Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information from the study.

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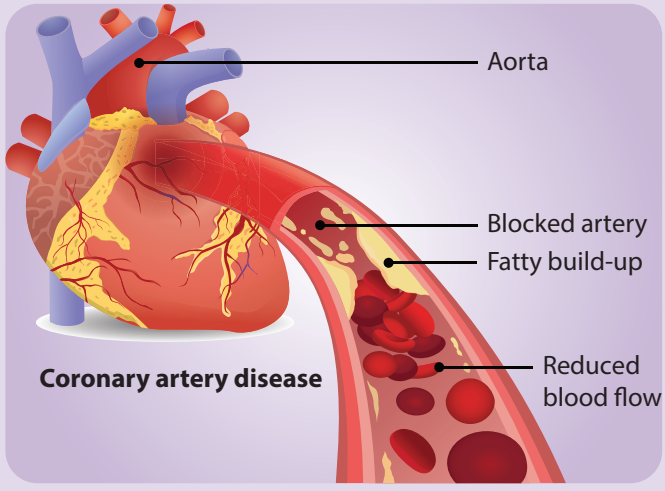
What is FH?

Familial hypercholesterolemia (also called FH) is a genetic disorder that affects the way cholesterol is processed by the liver. Cholesterol is carried through the blood as round particles called lipoproteins, which include LDL-C and HDL-C. In people with FH, the liver doesn't process cholesterol very well, so LDL-C levels can build-up in the blood.

High levels of LDL-C can cause the build-up of fatty deposits in people's coronary arteries, which are blood vessels in the heart. This gradual increase in fatty deposits over time narrows the arteries and is called **atherosclerosis**. When this happens, serious health problems can occur such as **coronary heart disease** (if it affects arteries to the heart), stroke (if it affects arteries to the brain), or peripheral vascular disease (if it affects arteries to the extremities such as arms, legs, hands, and feet), which may develop at an early age. **Heart valve disease** caused by **supravalvular aortic stenosis** is also seen frequently in people with FH, and involves narrowing of the aortic above the aortic valve.

FH is caused by one or more faulty genes and is passed down through families. Most children with FH inherit a faulty gene from one parent, and this is known as **heterozygous FH (HeFH)**. Sometimes a child will inherit faulty genes from both parents, and this is known as **homozygous FH** (HoFH). HoFH is much rarer, but it is also much more severe than HeFH.

Low-density lipoprotein (LDL) particles carry LDL-C, which is commonly called 'bad' cholesterol. When the body is working correctly, LDL particles are removed from the blood by liver cells. These liver cells have small pieces sticking out on their surface called LDL receptors, which 'catch' the LDL particles in the blood and take them inside the cell where the LDL-C present in the LDL can be used, stored, or broken down. People with HoFH typically do not have LDL receptors, or the receptors do not work properly, so the receptors in the liver are unable to 'catch' the LDL-C circulating in the blood and remove it from their body. LDL receptor genes with an error in the **DNA** code are the most common cause of HoFH (85–90% of cases), but there are other types of faulty genes associated with HoFH including the *APOB* gene and the *PCSK9* gene. Both of these faulty genes play a role in stopping the LDL receptor working effectively.



Atherosclerosis: Build-up of fatty material inside arteries.
Coronary heart disease: A type of heart disease where the coronary arteries (blood vessels in the heart) become narrowed by a build-up of fatty material within their walls, reducing the supply of oxygen-rich blood to the heart.
Heart valve disease: Occurs when one or more valves in the heart don't function properly, leading to problems with blood flow.
Supravalvular aortic stenosis: A narrowing (stenosis) of aorta, the large blood vessel that carries blood from the heart to the rest of the body.
Heterozygous: An inherited gene from one parent only.
Homozygous: The same inherited gene from both parents.
DNA: Is a molecule that is present in every cell in your body and contains information like an instruction manual for making the body work properly.



HoFH can be diagnosed by:

1) Genetic testing.
2) A physical exam and cholesterol levels.

People are told they have HoFH when the genetic test is positive or when LDL-C levels become very high and reach a certain level. Additional diagnostic criteria are needed for diagnosis in these cases, not just high LDL-C levels.

How many people have HoFH?

HoFH is very rare and affects around **1 in 250,000 to 360,000 people worldwide**. This is approximately 3 to 4 people in every million.

What are the symptoms of HoFH?

The build-up of cholesterol can cause signs and symptoms such as **exercise-induced chest pain (angina) secondary to coronary artery disease**, tendon xanthomas, xanthelasmas, and corneal arcus.

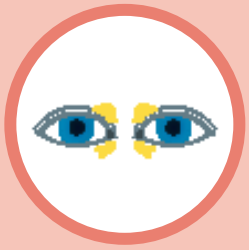
Exercise-induced chest pain (angina) secondary to coronary artery disease: Due to narrowed arteries the heart doesn't get enough oxygen during physical activity, leading to chest pain and/or discomfort.

Tendon xanthomas



Swollen knuckles, knees, or Achilles tendon at the back of the ankle

Xanthelasmas



Build-up of small lumps of pale yellow cholesterol in the skin at the bottom of the eyes and on the eyelids

Corneal arcus



A pale white ring around the outer edge of the cornea (the clear layer at the front of the eye) where the iris (the colored part of the eye) meets the sclera (the white part of the eye)

What treatments are available for people with HoFH?

People with HoFH are usually treated with a number of different medicines. Medicines called statins are used to help lower LDL-C levels. Statins are the most common treatment and are prescribed first. Statins do not work well for everybody, and some people have bad reactions to them, so other drugs are also needed alongside or instead of statins. These can include drugs such as ezetimibe, also called **PCSK9 inhibitors**, and lomitapide.

PCSK9 inhibitors and statins have little or no effect in people with HoFH who have certain types of gene variants like **non-null** and **null-null** genes. None of these are approved for children under the age of 8 years (lomitapide is not approved for people under the age of 18 years). Even for people for whom statins and PCSK9 inhibitors have an effect, they still work less well in people with HoFH so alternative therapies are also needed.

PCSK9 (also called proprotein convertase subtilisin/kexin type 9): A protein that has a crucial role in regulating cholesterol and lipid levels in the blood.
PCSK9 inhibitor (also called proprotein convertase subtilisin/kexin type 9 inhibitor): A treatment which helps to regulate lipid levels by stopping PCSK9 from working.
Non-null variant gene: A part of a person's DNA that has an error in it. The DNA can still work, but not completely effectively.
Null-null variant gene: A part of a person's DNA that has an error in it, meaning it cannot function correctly.

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Lipoprotein **apheresis** is a medical procedure that can be used in patients from the age of about 3 years. It involves taking some of the blood out of the body to remove LDL-C before returning the blood to the body. A limitation of lipoprotein apheresis is that it is a treatment that needs to be re-done on a regular basis e.g., weekly. It is also not available for all because the treatment is only carried out in highly specialized centers in many countries.

Apheresis: A type of treatment where blood from the body is filtered through a machine. The machine removes the excess lipoprotein from the blood and returns it to the body.

Where is evinacumab available?

- In **Canada**, evinacumab is used to treat HoFH as an add-on to diet and other LDL-C–lowering therapies in adults and children aged 5 years and older. In the **UK** and **European Union/European Economic Area**, evinacumab is approved for people with HoFH aged 6 months and above.
- In the **USA**, evinacumab is approved as an add on to other LDL-C–lowering therapies for the treatment of HoFH in patients aged 5 years or older.
- It is approved in **Japan** for all ages for the treatment of HoFH. More recently, evinacumab has been approved in **Brazil** and **Israel**.

What is evinacumab and how does it work?

Evinacumab is a **monoclonal antibody** that binds to a protein called angiopoietin-like 3, also called ANGPTL3. ANGPTL3 is produced by the liver and released into the bloodstream, where it helps to monitor the breakdown of lipids in the body. When evinacumab binds to ANGPTL3 it stops it from working, so more **lipids** can be broken down which in turn reduces the levels of LDL-C in the blood.

Evinacumab is given by **intravenous infusion** at a dose of 15 milligrams per kilogram of body weight (15 mg/kg) monthly (every 4 weeks).

Monoclonal antibody: An antibody is a kind of protein that the body's immune (defence) system normally makes to fight bacteria and viruses. Scientists can make copies of antibodies in the laboratory for the treatment of many different diseases, and these are called monoclonal antibodies.
Lipid: A fatty, waxy, or oily compound that is essential to many body functions and is a key component in all living cells.
Intravenous infusion: The slow injection of fluid into a vein.

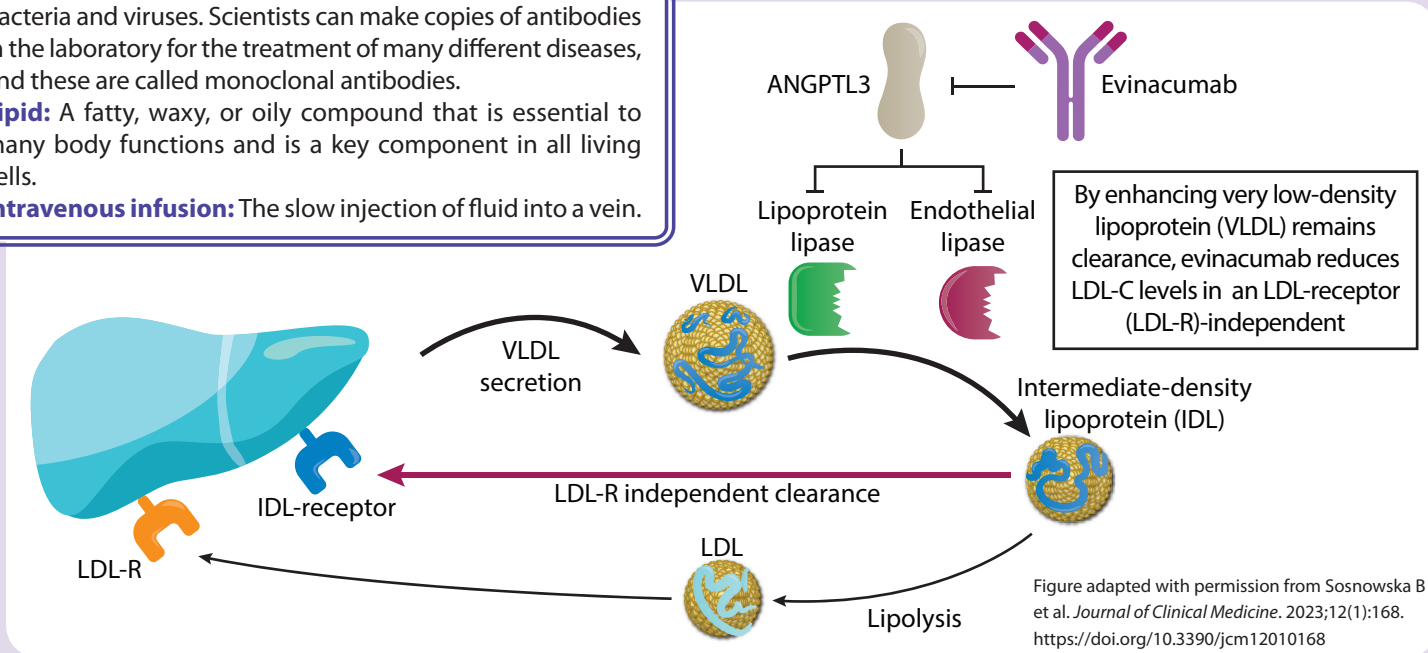


Figure adapted with permission from Sosnowska B et al. *Journal of Clinical Medicine*. 2023;12(1):168. https://doi.org/10.3390/jcm12010168

Why was the study carried out?

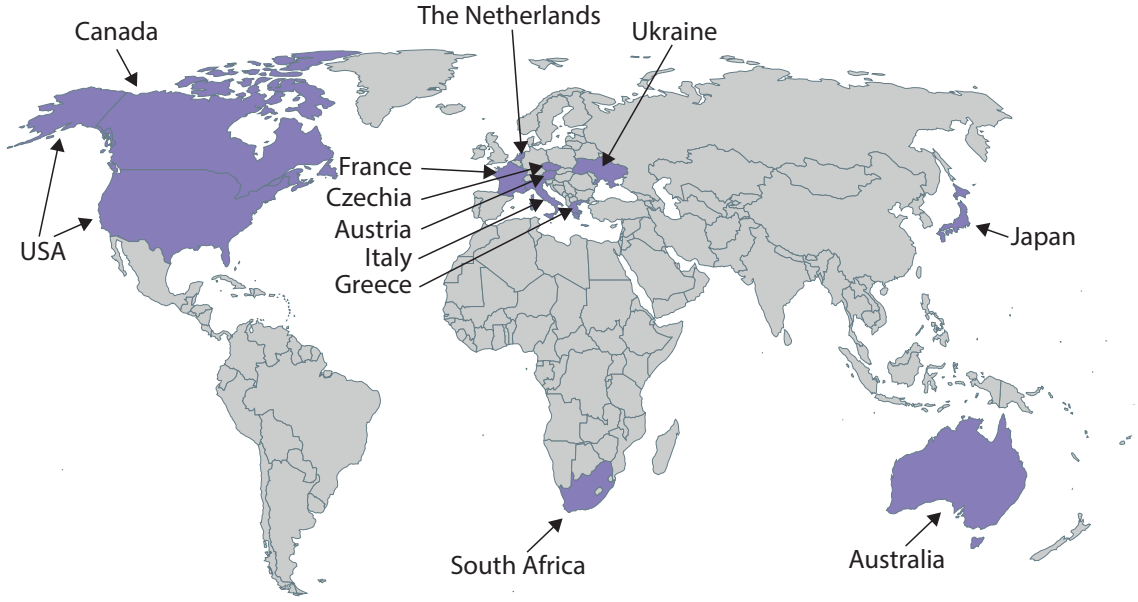
This is a key study that was carried out to assess the long-term safety and effectiveness of evinacumab in people with HoFH. Attempts to lower LDL-C in people with HoFH often require multiple treatments called **lipid-lowering therapies** to lower their levels of LDL-C in their blood. However, traditional treatments to lower LDL-C usually do not reduce LDL-C levels enough. This means there is an unmet clinical need for effective treatments that lower LDL-C in alternative ways.

Based on findings from clinical studies, evinacumab was first approved by the US Food and Drug Administration (FDA) in February 2021 and the European Medicines Agency (EMA) in June 2021 to treat people with HoFH aged 12 years and older as an add-on to other LDL-C-lowering therapies. However, more studies were needed to support the long-term use of evinacumab. This resulted in a key study looking at the long-term use of evinacumab in people aged 12 years and older diagnosed with HoFH. Another clinical study was conducted that showed evinacumab also worked in children aged 5–12 years (the full article is available for free at: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.123.065529).

Lipid-lowering therapy: Connect with the existing treatments patients have taken in the study to make it more comprehensive.

Where did the study take place?

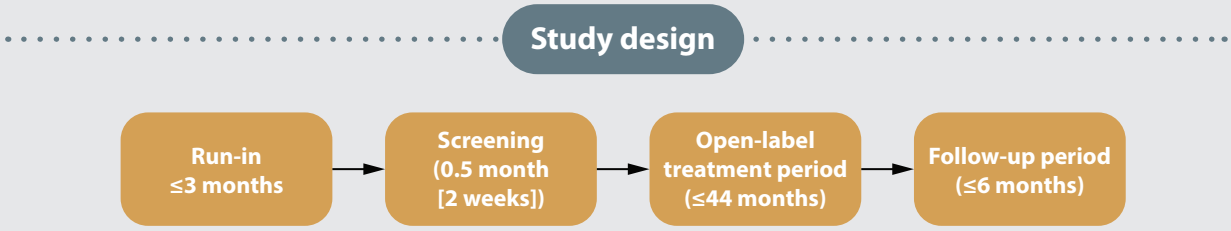
The study was carried out at 38 different medical sites across 12 countries.



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What happened in the study?

This pivotal Phase 3 study was conducted as 'open-label', which means that doctors, researchers, and participants knew what study drug people were receiving. In the study all participants who took part received 15 mg/kg of evinacumab.



Run-in: A period in a clinical study where all people included in the study either receive a drug or do not receive a drug.
Screening: A period in a clinical study where people included in the study undergo tests to determine their eligibility for the study.
Follow-up: The time after participants receive a treatment or no treatment during the clinical study to check the long-term effects of the treatment and to monitor any side effects.

What did researchers want to find out?

The aims of this long-term study were to find out:

- The type and severity of reported medical problems, also known as TEAEs, people had following up to 44 months of treatment with evinacumab.
- Whether evinacumab treatment for up to 44 months could lower LDL-C levels below the level people had at the start of the study (called baseline). Researchers also wanted to know whether evinacumab lowered other lipid levels, including apolipoprotein (also called **apoB**), **non-HDL-C**, **total cholesterol**, and lipoprotein(a) (also called **Lp(a)**).

ApoB: Moves fat throughout the body and helps fat to get through the wall of the arteries.
Non-HDL-C: The amount of cholesterol without the 'good' -C in your blood.
Total cholesterol: The overall amount of cholesterol in your blood, worked out by adding together the levels of HDL-C, LDL-C, and 20% of the **triglyceride** level.
Triglyceride: A type of lipid in the blood that is stored in fat cells. It is the most common type of lipid in the blood.
Lp(a): A lipid particle that accelerates damage caused by other risk factors including cholesterol.

Who took part in the study?

People diagnosed with HoFH who were aged 12 years and older, and who had LDL-C levels higher than 130 mg/dL (3.4 mmol/L) despite treatment with lipid-lowering therapies, were included in the study.

People were able to take part even if they had taken part in previous evinacumab studies. A full list of the criteria people had to meet to take part in the study can be found in the original article (the full article is available for free at: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.123.065529).

What were the main findings of the study?

116
people were included in the study

The average age was
12 to 17 years: 14 participants
18 to 44 years: 65 participants
45 to 64 years: 28 participants
65 to 74 years: 8 participants
75 years or older: 1 participant

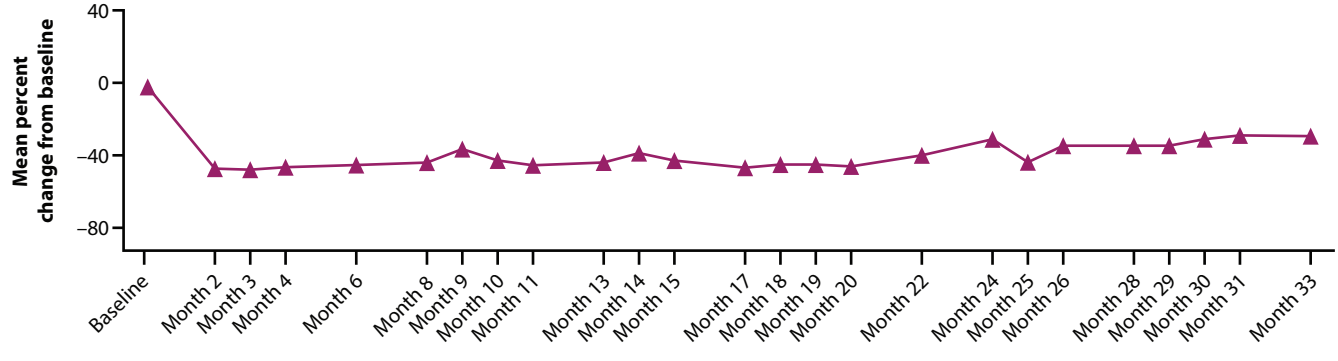
38.8 years

49.1%
About half were female (57 participants)

People in the study had between 6 and 45 months of treatment with evinacumab

Were LDL-C levels lower after 6 months of evinacumab treatment?

- On average, evinacumab treatment lowered LDL-C levels by nearly half (43.6%) in the first 6 months of the study from baseline. These reductions were maintained with long-term use of evinacumab until 28 months of the study. Although 82 people stopped participating in the study after 28 months due to the COVID-19 pandemic, which made assessing the results difficult, the reduction in LDL-C seemed to be maintained.



- When looking at the results by age of the 86 people in the study at Month 6, LDL-C was reduced by 41.7% in the adult group (aged 18 years or older, group size of 74) and by 55.4% in the adolescent group (aged 12–17 years, group size of 12).
- Reductions in LDL-C levels at Month 6 were similar whether people had taken evinacumab before or not: in the 55 people who had taken evinacumab before, the reduction was 41.3%; in the 31 people who had not taken evinacumab before, the reduction was 47.8%.

Reductions in LDL-C at Month 6 were observed with evinacumab treatment in different patient subgroups

55% in people aged 18 years or younger versus **42%** in those aged 18 years or older	Age	Sex	**51%** in females versus **37%** in males
42% in Caucasian people versus **48%** in non-Caucasian people	Race	DNA	**48%** in people with null-null variant genes and **41%** in those with non-null variant genes
39% in people receiving apheresis versus **46%** in those who were not	Apheresis	PCSK9 inhibitor	**46%** in people receiving a PCSK9 inhibitor versus **40%** in those who were not
47% in people receiving ezetimibe versus **27%** in those who were not	Ezetimibe	Statin	**43%** in people receiving statin versus **48%** in those who were not
52% in people receiving lomitapide versus **42%** in those who were not	Lompitapide	Baseline Lp(a)	**45%** in people with baseline Lp(a) less than 75 nmol/L (considered normal) versus **42%** in those with baseline Lp(a) 75 nmol/L or above

The non-Caucasian group consisted of people who self-reported as African American or Black, Asian, and other (including those who did not self-report as African American or Black, Asian, American Indian, or Alaska Native, Native Hawaiian or other Pacific Islander). It also included people for whom race was not reported.

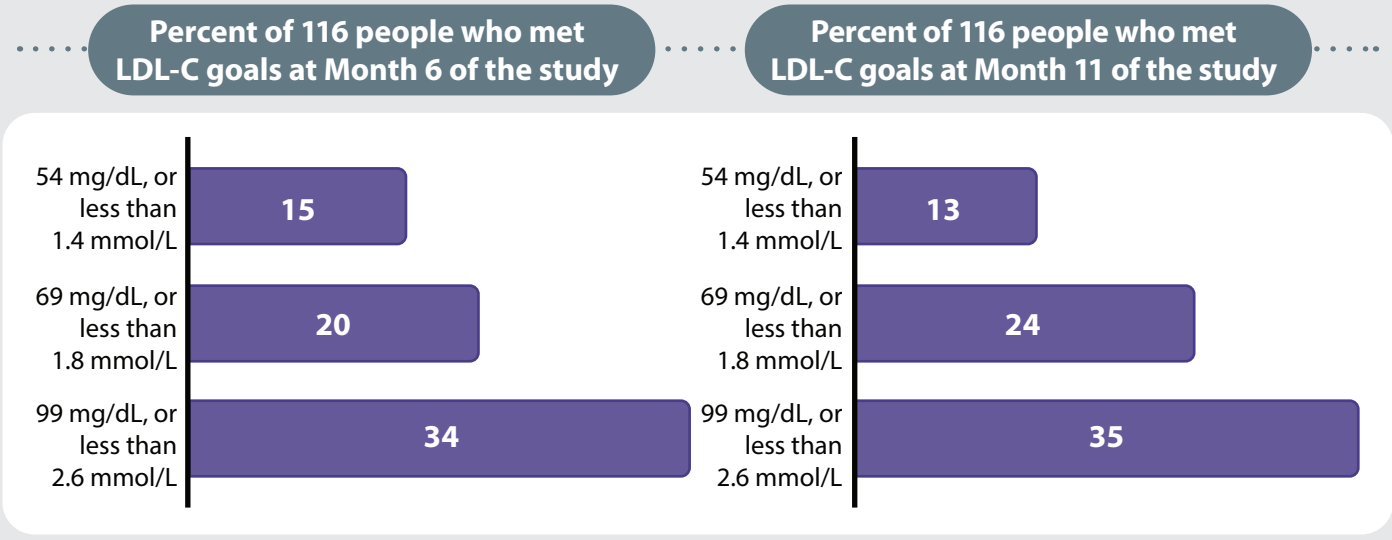
Ezetimibe, statins, and lomitapide: Types of lipid-lowering treatment that regulate lipids and reduce LDL-C.

Did evinacumab enable people in the study to meet LDL-C goals?

- Researchers and doctors have developed guidelines that recommend realistic and healthy LDL-C levels or goals that people with HoFH should aim to reach. This goal is the amount of LDL-C within a certain volume of blood.
- If possible, people with HoFH and **atherosclerotic cardiovascular disease**, or **ASCVD**, are advised to keep their LDL-C below 55 mg/dL (<1.4 mmol/L) or below 70 mg/dL (<1.8 mmol/L) if they do not have ASCVD. The lower the level of LDL-C, the better.
- At Month 6 of the study, evinacumab had enabled 34% of people with HoFH to reach the LDL-C level of under 100 mg/dL (<2.6 mmol/L), a level set by the recent European Society of Cardiology and European Atherosclerosis Society for people with HoFH to aim below, 20% had achieved the level of under 70 mg/dL (<1.8 mmol/L), and 15% had achieved the level of under 55 mg/dL (<1.4 mmol/L). By Month 11 of the study, 35% of people with HoFH had achieved the LDL-C level of under 100 mg/dL (<2.6 mmol/L), 24% had achieved the level of under 70 mg/dL (<1.8 mmol/L), and 13% had achieved the level of under 55 mg/dL (<1.4 mmol/L).

Atherosclerotic cardiovascular disease or **ASCVD:** A long-term condition that occurs when people have high levels of cholesterol in their blood.

Goals and levels of LDL-C can be measured in two different ways (mg/dL and mmol/L).



What were the results over the long term?

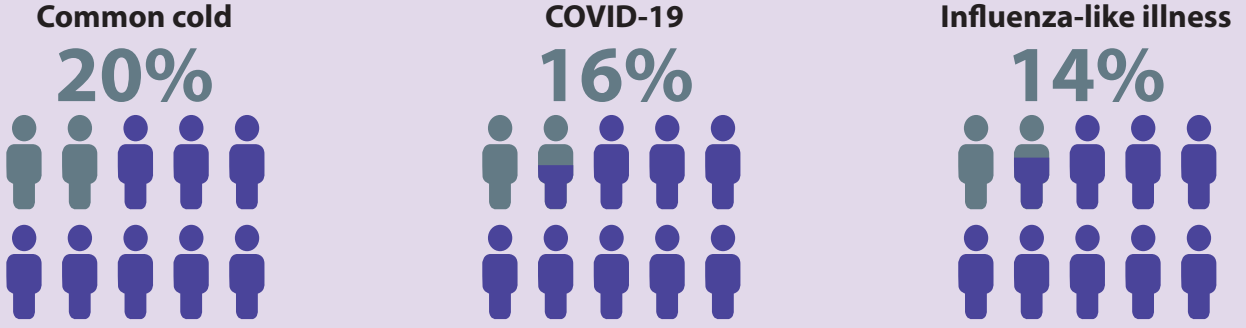
Although patient numbers varied at later points in the study due to the COVID-19 pandemic, the observed reductions in LDL-C were maintained throughout the study and to at least Month 33.

What happened to other lipid and lipoprotein levels after 6 months of evinacumab treatment?

- Lower levels of apoB, non-HDL-C, total cholesterol, and Lp(a) in the blood were seen starting at 6 months of treatment with evinacumab. These reductions continued until Month 28 of the study.

What TEAEs did people taking evinacumab have?

- During the study, 92 people (79%, or 8 in 10) reported medical problems. Most of these were mild (23% of TEAEs) or moderate (42% of TEAEs). The rest of the TEAEs (14%) were considered severe.
- Only 10 people (9%) experienced a medical problem that was considered to be related to the evinacumab treatment they received. People in the study may have experienced more than one medical problem.
- Three people (3%) discontinued the study. Two of these people were unable to continue in the study due to pregnancy. The third person had a headache during the study; the researchers/investigators did not consider this related to the study drug.
- The most commonly reported medical problems were:



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- Two people (2%) unfortunately died during the study. Both people had a long history of medical problems and experienced advanced HoFH. Both deaths were caused by serious medical problems involving the heart that are often expected in people with HoFH. These deaths were not considered by study doctors to be related to evinacumab treatment.

Side effect thought to be related to evinacumab	How many people were affected?
General weakness	2
Headache	2
Change of color in the mouth	1
Build-up of fluid in the face	1
Feeling hot	1
Redness at the injection site	1
Abnormal liver function	1
An infection of the lungs	1
Decreased blood sugar levels	1
Increased levels of some liver enzymes called transaminases	1
Muscle spasms	1
Less sensitive to pain	1
Abnormal feeling of the skin like pins and needles	1
Acne	1
Itching	1
Swelling of the face	1

What do the results of this study mean?

- The results from this study show that evinacumab treatment over 2 years effectively lowered levels of LDL-C and other lipids in people with HoFH.
- Adding evinacumab to existing lipid-lowering therapies further lowered LDL-C levels in adults and adolescents with HoFH.
- Evinacumab was generally well tolerated in people with HoFH aged 12 years and older.
- Evinacumab appears to be a useful therapy for long-term management of HoFH.

Where can I find more information?

Original article: 'Evinacumab in homozygous familial hypercholesterolaemia: long-term safety and efficacy', *Eur Heart J.* 2024;45(27):2422-2434. doi: 10.1093/eurheartj/ehae325.
You can access the full article for free at: https://academic.oup.com/eurheartj/article/45/27/2422/7689553

You can also find more about this study on the ClinicalTrials.gov website at: https://clinicaltrials.gov/study/NCT03409744
Study start date: 13 March 2018
Study end date: 13 April 2023

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