Future
CARDIOLOGY

ISSN: 1479-6678

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Reprinted from:
Future Cardiol. 2025;21(3):139-147. doi: 10.1080/14796678.2025.2461425

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Plain Language Summary of Publication

Evinacumab for children with homozygous familial hypercholesterolemia: a plain language summary

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First draft submitted: 12 June 2024; Accepted for publication: 29 January 2025

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

The original article is called 'Evinacumab for Pediatric Patients with Homozygous Familial Hypercholesterolemia', and has been published in the journal *Circulation*. You can read it for free at: https://www.ahajournals.org/doi/epdf/10.1161/CIRCULATIONAHA.123.065529.

Summary

What is this summary about?

This is a plain language summary explaining the results of a study assessing a treatment, called evinacumab, for children with a condition called homozygous familial hypercholesterolemia, also known as HoFH. HoFH is a rare **genetic disorder** that makes the liver less able to remove 'bad' **cholesterol** (called **low-density lipoprotein cholesterol**, or LDL-C) from the body. High levels of LDL-C increase the risk of early development of serious heart problems. Only a small number of options are available to treat children with HoFH, and these do not always work well. Evinacumab is approved in the European Union, United Kingdom, Canada, and the USA as the first medicine approved for children with HoFH aged 5 to 11 years as an add-on to other therapies that lower LDL-C. In Japan, evinacumab is also approved for treatment of people with HoFH when given with other LDL-C-lowering therapies. Evinacumab was recently approved to treat HoFH in Brazil and Israel.

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

- **Atherosclerosis:** ATH-er-o-SCLER-o-sis
- **Cholesterol:** KOL-est-er-ol
- **Evinacumab:** EH-vin-A-cue-mab
- **Homozygous familial hypercholesterolemia:** ho-muh-zi-gus FAM-ee-li-al hi-per-kuh-le-stuh-ruh-lee-mee-a

What were the results of the study?

Children with HoFH aged 5 to 11 years treated with evinacumab every 4 weeks for 24 weeks had LDL-C levels in their blood that were almost half what they were before treatment was started. The reduction in LDL-C was seen as early as 1 week after treatment was started and was maintained through 24 weeks of treatment. Overall, evinacumab was generally well accepted by most of the children in the study. **Side effects** were similar to those seen in adults and adolescents with HoFH. The most common side effects in children were throat pain, stomach pain, diarrhea, nausea, vomiting, headache, and symptoms like those seen in a common cold.

What do the results mean?

This study showed that evinacumab lowered 'bad' cholesterol in children of 5 to 11 years with HoFH.

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 and low-density lipoprotein 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.

Side effect: An unwanted or unexpected bad reaction to a drug.

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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.

Who is this article for?

This article may be helpful to families or caregivers of children with HoFH. 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 **sponsor** was Regeneron Pharmaceuticals, Inc.

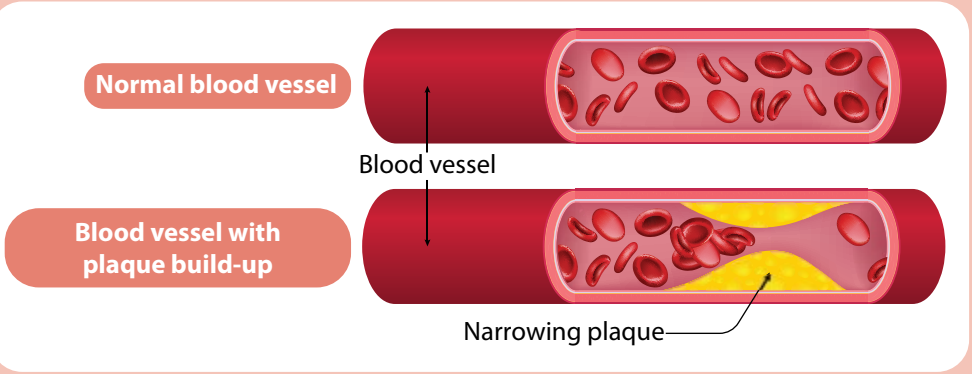
Sponsor: A company or organisation that oversees and pays for a clinical research study. The sponsor also collects and analyses the information from the study.

What is HoFH?

Familial hypercholesterolemia (also called FH) is a genetic disorder that affects the way the liver deals with cholesterol.

Cholesterol is transported around the body as **lipoproteins**, including LDL-C and high-density lipoprotein cholesterol (HDL-C). If the liver is not dealing with cholesterol properly, as in FH, LDL-C levels can build up in the blood. High levels of LDL-C can cause fatty materials, or **plaques**, to gradually build up in people's blood vessels in the heart. This build-up can lead to narrowing of the arteries and serious heart problems at an early age.

FH is caused by faulty genes that can be passed down from one or both parents. Most children with FH inherit a faulty gene from one parent, and this is known as heterozygous FH. 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.



HoFH can be diagnosed by:

- Testing a person's genes
- Looking at a person's cholesterol levels together with an examination by a doctor

People are told they have HoFH when the genetic test is positive or when cholesterol levels become very high.

Lipoprotein: A substance that is made up of both lipid (fat) and protein; lipoproteins carry cholesterol around the body through the blood.
Plaque: A build-up of fats, cholesterol, or other substances in and on the walls of blood vessels.

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LDL-C is often called 'bad' cholesterol. Normally, it is removed from the blood by the liver. Liver cells have small extensions on them called low-density lipoprotein (LDL) receptors which 'catch' the LDL-C in the blood and take it into the cell to be used, stored, or broken down. Most people with HoFH either do not have LDL receptors, or the receptors do not work properly, so they are unable to 'catch' LDL-C and remove it from the body.

Faulty LDL receptor genes are the most common cause of HoFH (85–90% of cases), but there are other faulty genes associated with HoFH. These include the APOB gene, which is a sequence of DNA that makes apolipoprotein B (apoB), a lipoprotein that reduces the LDL receptor's ability to bind to cholesterol; and the PCSK9 gene, which leads to LDL receptors being deactivated in the liver.

How many people have HoFH?

HoFH is very rare and affects around **1** person in every **250,000** to **360,000** worldwide.

What are the symptoms of HoFH?

The build up of cholesterol can cause symptoms that can be seen by a doctor.

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 iris (the colored part of the eye)

What treatments are available for people with HoFH?

People with HoFH are usually treated with medicines called statins, which help to lower cholesterol levels. Other medicines that can be used alongside or instead of statins include ezetimibe, PCSK9 inhibitors, and lomitapide. Not all of these medicines work well in people with HoFH, and none are approved for children younger than 8 years (lomitapide is not approved for people younger than 18 years). Another way to lower cholesterol in the blood is a medical process called lipoprotein apheresis. This involves taking some of a person's blood outside of their body to remove LDL-C before returning the blood to their body. Apheresis can be used in children with HoFH from about 3 years of age, but the treatment needs to be repeated at regular intervals. Apheresis is not available for all children.

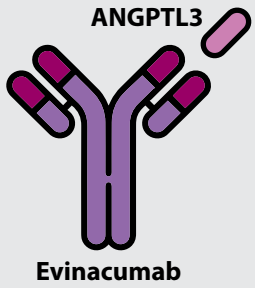
Young children with HoFH have very limited treatment options.

What is evinacumab and how does it work?

In many countries, evinacumab is added to other LDL-C-lowering therapies in adults and children aged 5 years and older with HoFH.

Evinacumab is a **monoclonal antibody** that binds to a protein called angiopoietin-like 3, also known as ANGPTL3. ANGPLT3 is involved in the process that helps break down **lipids** in the body. When evinacumab binds to ANGPTL3 it stops ANGPTL3 from working, and this lowers LDL-C.

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



Monoclonal antibody: A kind of protein that a person's immune (defense) system makes to fight bacteria and viruses. Scientists can make antibodies in the laboratory, and these can be used to treat many different diseases.
Lipid: A fatty, waxy, or oily substance that is needed for many body functions and acts as the building block for all living cells.
Intravenous infusion: The slow injection of fluid into a vein.

Why was the study carried out?

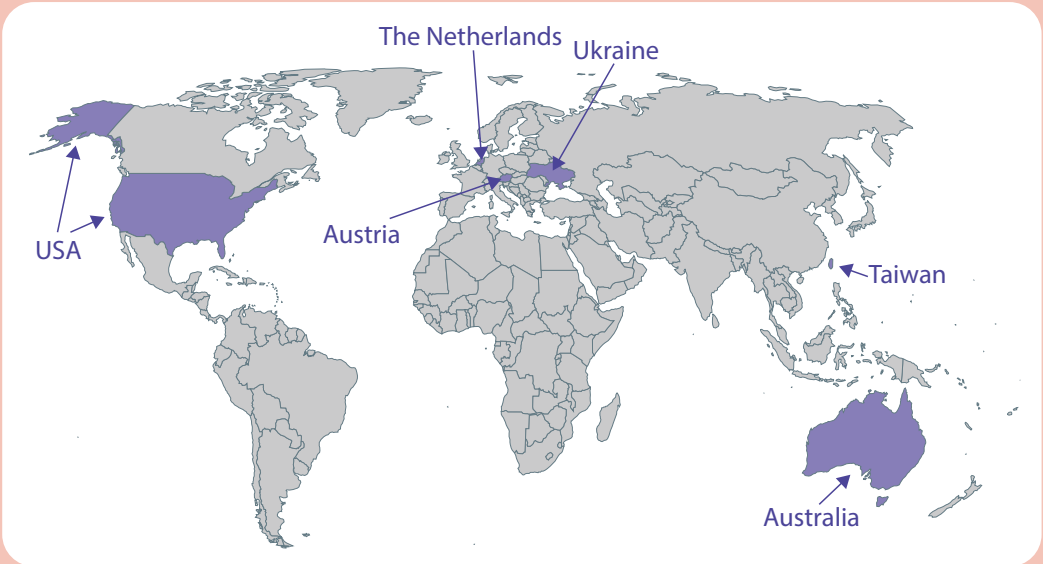
There are few medicines for children with HoFH.

Evinacumab was 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 are needed to support the use of evinacumab in children younger than 12 years.

The current study investigated evinacumab in children with HoFH aged 5 to 11 years. Based on the results of this study, evinacumab was approved by the FDA in March 2023 and the EMA in December 2023 for children with HoFH aged 5 to 11 years when added to other LDL-C-lowering therapies.

Where did the study take place?

The study was carried out at 10 different hospitals across the six countries shown in the figure.



What happened in the study?

The study was split into three parts.

- The first part (called a **phase 1b** study) looked at how safe evinacumab was, how evinacumab moved around the body and what the body did to it, and how evinacumab worked to treat HoFH. Six children in this part each received a single intravenous infusion of evinacumab at a dose of 15 mg/kg. The children were checked for 16 weeks after receiving the evinacumab dose.
- The second part (called a **phase 3** study) looked at the **efficacy**, safety, and what the body did to evinacumab. In this part, 14 children received evinacumab at 15 mg/kg every 4 weeks for 24 weeks and were checked during this time.
- The third part was also a phase 3 study and looked at safety and efficacy of evinacumab for a longer time. All of the children who took part in the first two parts of the study are included in the third part of the study. They received evinacumab at 15 mg/kg every 4 weeks for 48 weeks. At the end of treatment, the children were checked for another 24 weeks.
- The results for the third part will be reported in a separate article and Plain Language Summary.

Phase 1b: A clinical study that usually tests the safety of a treatment in a small number of healthy people or people with the specific condition.
Phase 3: A clinical study carried out in a larger number of people with the specific condition to test how well the treatment works and if there are any side effects.
Efficacy: How well a treatment works.

How was this study carried out?

First part: Phase 1b, 16 weeks

Aims of the first part:

- Test the safety of evinacumab
- Check how evinacumab moves around the body and what the body does to it
- Check whether the 15 mg/kg dose is suitable for children, therefore allowing the use of this dose in the second part

Second part: Phase 3, 24 weeks

Aims of the second part:

- Test the safety of evinacumab
- Check how well evinacumab lowered blood levels of LDL-C and other lipids

Run-in: A time period at the start of a study when the researchers make sure that the participants can follow the rules of the study.
Screening: A time period that the researchers use to make sure the participants meet all criteria to join the study.
Open-label treatment period: This is a period of time in the study when both the researchers and participants know what study drug they are taking.
Observation period: A time period after treatment has ended when researchers can keep track of any changes in the participants behavior or symptoms that may last a longer time.

What did researchers want to find out?

- In the first part of the study, researchers were looking at how evinacumab moves through the body and the actions of the body on evinacumab specifically in children.
- In the second part, researchers wanted to see whether the LDL-C levels were lower after 24 weeks of treatment with evinacumab than they were at the start of the study (called baseline). They also wanted to know whether evinacumab lowered other types of lipid and lipoproteins in the blood, including **apoB**, non-high-density lipoprotein cholesterol (**non-HDL-C**), **total cholesterol**, and lipoprotein(a) [**Lp(a)**].
- In both parts, researchers wanted to see whether children taking evinacumab had any side effects.

ApoB: A lipoprotein that helps carry cholesterol through the blood.
Non-HDL-C: The amount of 'bad' cholesterol in the blood.
Total cholesterol: The overall amount of cholesterol in the blood.
Lp(a): A large lipoprotein that helps carry cholesterol through the blood.

Who took part in the study?

- Children with HoFH aged 5 to 11 years and who had LDL-C levels higher than 130 mg/dL (normal LDL-C levels are less than 100 mg/dL), even though they were already receiving treatment with **lipid-lowering therapies**, were included in the study.
- Six children were included in the first part of the study and 14 children were included in the second part. Among the children who took part in the second part of the study, half were receiving lipoprotein apheresis treatment and 29% were found to have no active LDL receptors.

Lipid-lowering therapies: A drug that lowers lipid levels in the blood.

First part (6 participants)

The average age was **8.8** years

67% were female (four participants)

100% were white (all six participants)

Second part (14 participants)

The average age was **9.1** years

57% were female (eight participants)

5.4 The average length of time since diagnosis of HoFH was 5.4 years

29% had no active LDL receptors

50% were receiving lipoprotein apheresis treatment

264 mg/dL **6.8 mmol/L** The average LDL-C level at the start of the study

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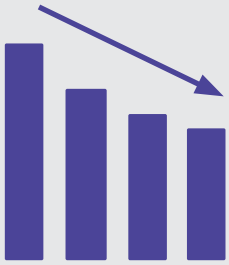
What were the main findings of the study?

How did the body handle evinacumab?

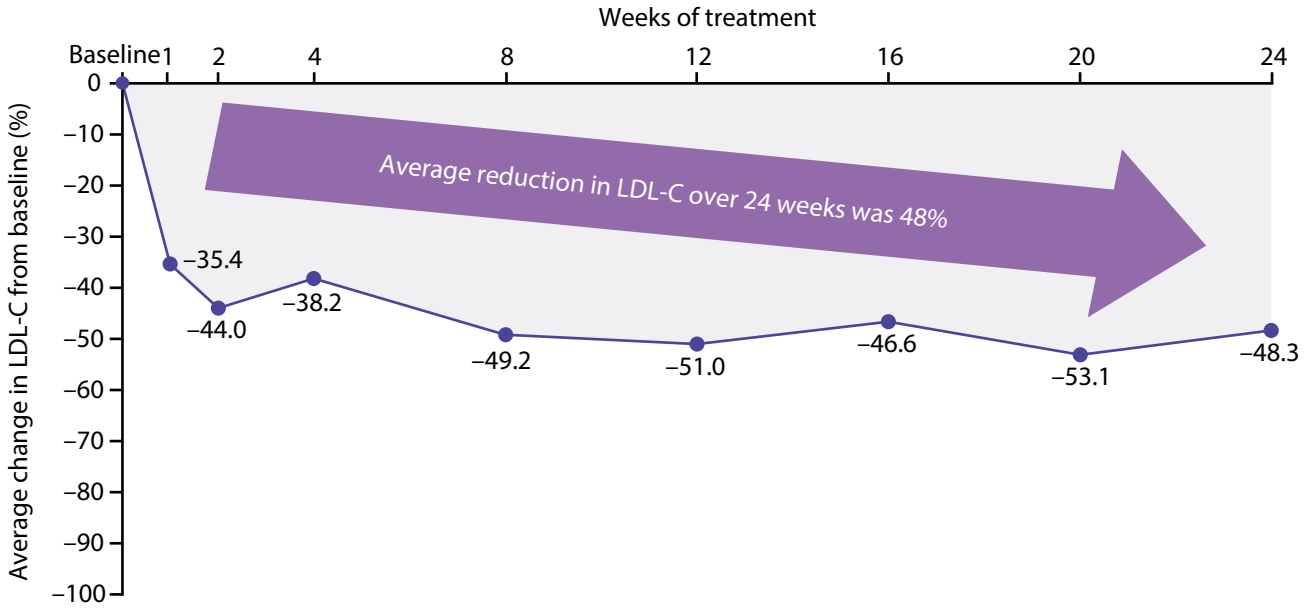


In the six children who received a single dose of evinacumab in the first part of the study, levels of evinacumab in the blood reduced over time in a similar way to that seen in adolescents and adults.

This was important because it confirms that a 15 mg/kg intravenous dose is suitable for children aged 5 to 11 years, as well as for older people.

Were LDL-C levels lower after 24 weeks of evinacumab treatment?

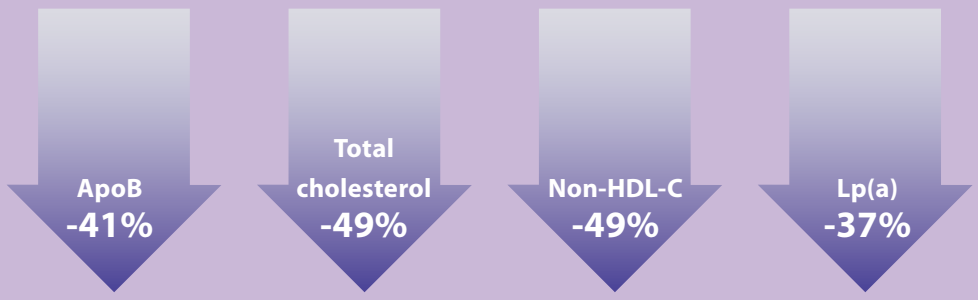
- Evinacumab treatment rapidly lowered LDL-C levels during the first week of treatment in the 14 children in the second part of the study. After 24 weeks of evinacumab treatment, the average LDL-C levels dropped by almost half (48%).
- The researchers looked at how well certain patients did on treatment and found similar results among the four children who had no active LDL receptors who had a 46% drop in LDL-C.
- Average LDL-C levels were also lowered by about half in the seven children who were receiving lipoprotein apheresis treatment and the seven children who were not receiving lipoprotein apheresis treatment.



What happened to other lipid and lipoprotein levels after 24 weeks of evinacumab treatment?

Reductions were also seen in levels of apoB, non–HDL-C, total cholesterol, and Lp(a) in the blood after 24 weeks of treatment with evinacumab. This is important because high levels of these substances can have harmful effects on the heart and blood vessels that carry blood all over the body.

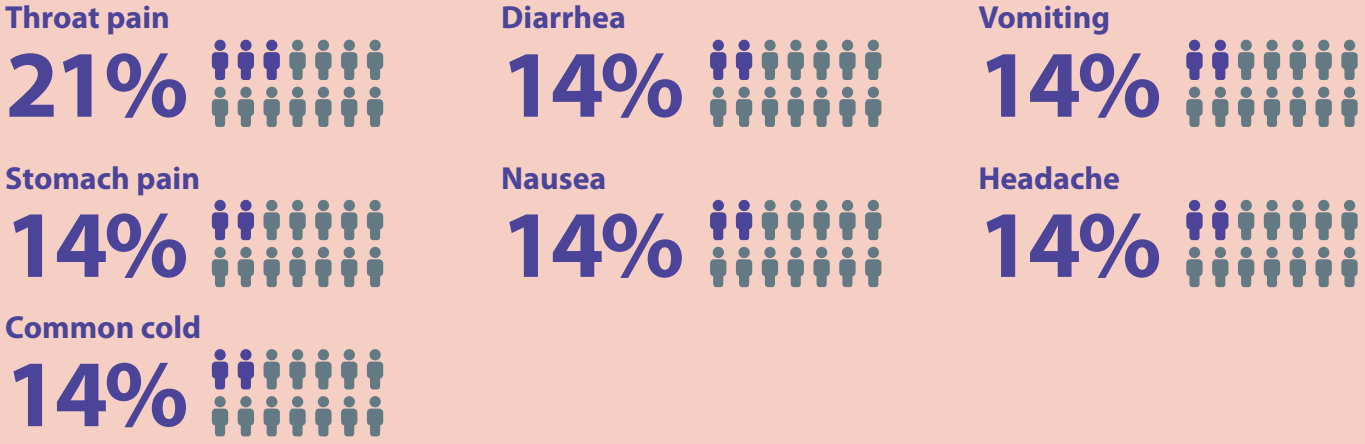
Average reduction after 24 weeks of evinacumab treatment



What side effects did children taking evinacumab have?

Most of the children (71%) in the second part of the study had a side effect while taking evinacumab.

The most common side effects in children who had a dose of evinacumab every 4 weeks were:



Serious side effects are side effects that might need hospitalization, could cause disability, or could result in death. One child had a serious side effect of tonsillitis. The doctors did not think that any of these side effects were caused by evinacumab. No participants experienced side effects that meant they had to stop treatment, and no deaths were reported during the study period.

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What do the results of this study mean?

- A 15 mg/kg intravenous dose of evinacumab is suitable for children aged 5 to 11 years.
- Adding evinacumab to other lipid-lowering therapies lowered LDL-C levels by nearly half in children aged 5 to 11 years with HoFH.
- Evinacumab also reduced other important lipid and lipoprotein blood levels, such as apoB, non-HDL-C, total cholesterol, and Lp(a).
- Evinacumab was generally well accepted in children aged 5 to 11 years with HoFH.
- Evinacumab appears to be a useful therapy for children with HoFH as young as 5 years old, and could help them to reach LDL-C levels that are recommended by doctors.

Were there any limitations with the study?

The study had some limitations. First, the open-label study design means that participants and researchers knew what treatment they were receiving, and the results could not be compared with a separate group of participants that did not receive the treatment. Second, there was a small number of participants. Third, the participants were not checked for a very long time after the treatment ended.

Where can I find more information?

The original article of the study was published in *Circulation*: Wiegman A, *et al.* Evinacumab for Pediatric Patients With Homozygous Familial Hypercholesterolemia. *Circulation*. 2024;149(5):343–353. The study start date was June 29, 2020, and the completion data was May 30, 2023. The results of the third part of the study will be published in a separate article. You can access the full article for free here: https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.123.065529.

You can also find more about this study on the ClinicalTrials.gov website: https://clinicaltrials.gov/study/NCT04233918.

Acknowledgements

The authors thank the patients and their families for their participation in and support for this study.

Disclosure statement

Albert Wiegman reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Sanofi, Ultragenyx, Esperion, and Algorithm; participation in a data safety monitoring board or advisory board for Chiesi; leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid, for Novartis; and research support for pharmaceutical trials from Amgen, Regeneron Pharmaceuticals, Inc., Novartis, Silence Therapeutics, Esperion, and Ultragenyx. Robert Pordy is an employee of and stockholder in Regeneron Pharmaceuticals, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing support for this summary was provided by Alpha (a division of Prime, Knutsford, UK), and was funded by Regeneron Pharmaceuticals, Inc.

Patient reviewers on this PLSP have received honorarium from *Future Cardiology* for their review work but have no other relevant financial relationships to disclose.

Funding

This study was funded by Regeneron Pharmaceuticals, Inc. The study sponsor was involved in the study design and collection, analysis, and interpretation of data, as well as data checking of information provided in the article.