Clinical Trial Results – Layperson Summary

A study to look at the side effects of taking emicizumab in people with moderate or mild haemophilia A without inhibitors against factor eight – and how well emicizumab prevented bleeding

See the end of the summary for the full title of the study, and a hyperlinked glossary of medical terms. Hyperlinked terms are in **bold and underlined**.

About this summary

- This is a summary of the results of a **clinical trial** (called a 'study' in this document) – written for:
  - the adolescent and adult participants,
  - the general public, and
  - the caregivers of the children that took part in the study.

The study started in February 2020 and is expected to end in April 2023. This summary contains results from the main analysis carried out in October 2021 (when people had been part of the study for an average of 55.6 weeks). Before the main analysis, an interim analysis was carried out in April 2021 (when people had been part of the study for an average of 27.5 weeks). Some results from the interim analysis are also included in this summary. At the time of writing this summary, the study is still happening – study doctors are still collecting information.

No single study can tell us everything about the risks and benefits of a medicine. It takes many people taking part in several studies to find out what we need to know. The results from this study may be different from other studies with the same medicine.

- You should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

Contents of this summary

Thank you to the people who took part in this study

The people who took part in this study have helped doctors to answer important questions about haemophilia A and the study medicine – emicizumab.

1. General information about this study

What is haemophilia A?

Haemophilia A is a rare **inherited** bleeding disorder caused by an abnormal **gene** on the **X chromosome**. As a result, haemophilia A mostly affects men and boys; overall, around 3.5% of people with haemophilia A are female.

People with haemophilia A have little to no activity of a **protein** in the blood called 'clotting factor eight' (also seen as 'FVIII'). Without this active protein, the blood cannot clot normally. This means that people with haemophilia A can have many bleeds that can last for a long time, including in their joints and muscles. These bleeds can be caused by minor injuries or may have no obvious cause.

People with haemophilia A can be grouped based on how little factor eight they have. '**Severe**' haemophilia A means that people have factor eight activity less than 1% of the level observed in someone without haemophilia A. '**Moderate**' haemophilia A means that people have factor eight activity between 1% and 5% of the level observed in someone without haemophilia A, while '**mild**' haemophilia A means that people have factor eight activity of between 5% and 40% of the level observed in someone without haemophilia A.

How is haemophilia A treated?

One of the standard treatments for people with haemophilia A is to replace the missing or inactive factor eight protein with '**replacement factor eight**'. This treatment increases the amount of active factor eight in the blood, improving the ability of the blood to make clots. Replacement factor eight is given as an injection into a vein (sometimes called an '**IV injection**').

When replacement factor eight is given to help the bleeding stop only after a bleed has happened, this is called '**on-demand treatment**'.

Replacement factor eight can also be given on a regular basis to prevent bleeding. This type of preventative treatment is called '**prophylactic treatment**'.

When replacement factor eight is given to prevent bleeding, it must be given twice a week or more often. This is because replacement factor eight remains in the blood for a short period of time – exactly how short is dependent on how it is processed by each person's body, and the type of replacement factor eight treatment given.

There are many different types of replacement factor eight treatment. Different people may receive different doses. People with haemophilia A may be treated on demand or with prophylactic treatment.

What is the study medicine?

The study medicine is called 'emicizumab' (HEMLIBRA®). It is another type of treatment for haemophilia A.

- You say this as 'em – me – sih – zuh – mab'.

- Emicizumab acts as a substitution therapy for factor eight by acting on other clotting proteins found in the blood.
- Emicizumab improves the ability of the blood to make clots, which means that bleeding is less likely in people with haemophilia A.
- Emicizumab is a preventative (prophylactic) treatment. This means that it is given on a regular basis to prevent bleeding.
- Emicizumab is given as an injection under the skin (sometimes called '**subcutaneous injection**'). This is different than replacement factor eight treatment, which is given as an injection into a vein.

What do doctors want to find out?

Doctors are carrying out this study to look at side effects in people of all ages with moderate or mild haemophilia A without inhibitors against factor eight who are taking emicizumab (see section 4 "What side effects were reported in this study?").

Although it is not the main objective, this study is also looking at how many bleeds people with moderate or mild haemophilia A without inhibitors against factor eight have when taking emicizumab (see section 5 "What other results were reported in this study?").

What kind of study is this?

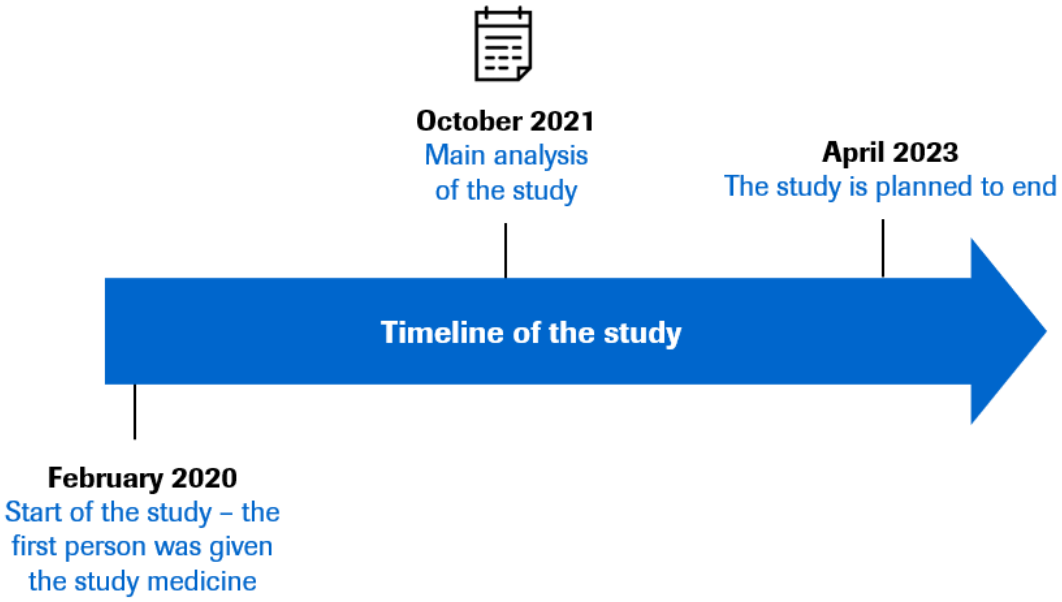
This study is a '**Phase 3**' study. If a new drug is shown to be effective and has a favourable **safety profile** in a Phase 3 study, the results can be used to gain approval from health authorities in different countries to make the drug available for doctors to give to patients.

This is an '**open label**' study. This means that both the doctors and the people who take part in the study know which medicine they are receiving.

Emicizumab is not being directly compared with any other medicine in this study.

When and where is this study taking place?

This study started in February 2020 and is expected to end in April 2023. This summary focuses on the results of the main analysis, up until October 2021 – over one year after the start of the study. At the time of writing this summary, the study is still ongoing – study doctors are collecting information and people taking part in the study are being monitored.



The calendar symbol on the timeline (📅) shows when the results in this summary were collected – October 2021 for the main analysis.

This study is taking place at 22 study centres across 10 countries. The following map shows the countries where the study is taking place.

- Belgium – 2 centres
- Canada – 2 centres
- France – 3 centres
- Germany – 2 centres
- Netherlands – 1 centre
- Poland – 1 centre
- South Africa – 1 centre
- Spain – 2 centres
- United Kingdom – 3 centres
- United States – 5 centres

2. Who is taking part in this study?

While this study planned to have 73 people participate, one person dropped out before they received emicizumab. In this study, at the time of the interim analysis (April 2021), 71 people with haemophilia A had taken part. At the time of the main analysis (October 2021), one additional person had taken part in the study, bringing the total to 72 people. Of these 72 people, 51 people had moderate haemophilia A and 21 people had mild haemophilia A. Most people in the study were male; with 69 males and 3 females. The age of people in the study ranged from 2 to 71 years.

People could take part in this study if they:

- Weighed 3 kg or more
- had a diagnosis of moderate or mild haemophilia A without inhibitors against factor eight
- had a clinical need for regular, preventative treatment (prophylactic treatment), as determined by their doctor
- had documentation on the number of bleeding events they had for at least 24 weeks before the start of the study.

People could not take part in the study if they:

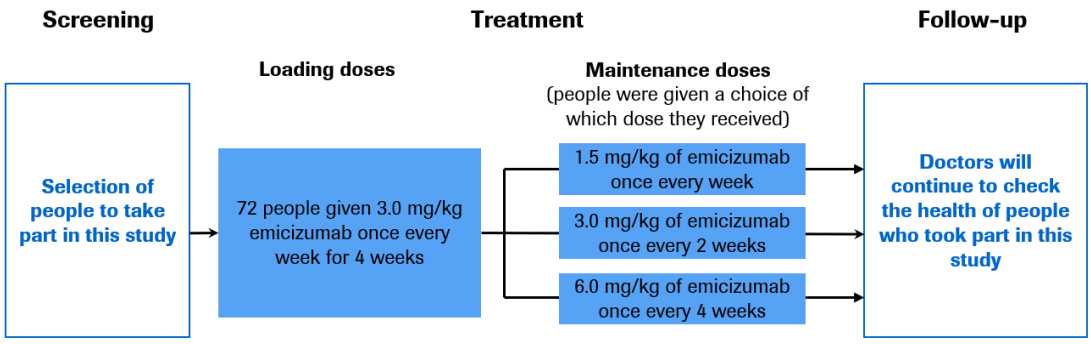
- had diseases or conditions other than haemophilia A that might have increased their risk of bleeding
- had treatment for blood clots in the previous 12 months.

3. What is happening during this study?

The 72 people in this study were first given 3.0 mg/kg of emicizumab once every week for 4 weeks to quickly build up the levels of emicizumab in the body ('**loading doses**').

After the first 4 weeks and with advice from their clinician, people were given the choice of receiving: 1.5 mg/kg of emicizumab once every week, 3.0 mg/kg of emicizumab once every 2 weeks, or 6.0 mg/kg of emicizumab once every 4 weeks ('**maintenance doses**').

At the time of the main analysis, most people in the study had taken emicizumab for approximately 1 year. This study is still ongoing at the time of writing this summary, so people are still being treated with the study medicine. When the study finishes, people taking part can continue to take emicizumab, or change to a different treatment if they prefer. Look below to see more information about what is happening in this study.



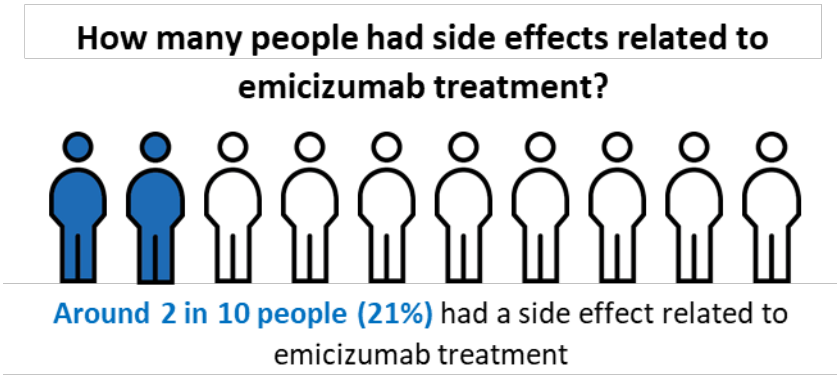
4. What side effects were reported in this study?

Question 1: What side effects did people have related to emicizumab?

Side effects (also known as 'adverse reactions') are unwanted medical problems (such as feeling dizzy) that happen during the study. They are described in this summary because the study doctors believe the described side effects were related to emicizumab treatment.

- Not all of the people in this study had side effects related to emicizumab.
- Side effects can vary from mild to serious and may vary from person to person.
- It is important to be aware that the side effects reported here may be different from those seen in other studies, or those that appear on the medicine leaflet.

At the time of the main analysis, a total of 15 out of 72 people (that is equal to 2 in 10 people, 21%) in this study had side effects related to emicizumab.



A side effect is considered '**mild**' if it causes mild discomfort, lasts less than 2 days, and no treatment is needed. A side effect is considered '**moderate**' if it causes mild to moderate limitations on the person's activity, may cause the person to need some assistance, and little or no treatment is needed.

Most of the side effects related to emicizumab were redness of the skin where the injection was given, called an '**injection site reaction**'. These were considered by the study doctors to be mild. At the time of the main analysis, 12 out of 72 people (17%) had reported injection site reactions that were side effects related to emicizumab treatment.

The table below lists all of the side effects related to emicizumab that had been reported at the time of the main analysis in this study. It also shows the number of people in the study who had each of these side effects. People could have more than one type of side effect.

Side effect	Number of people who had this side effect at the main analysis (out of 72 people)
Injection site reaction	12
Headache/head pain	12
Tiredness	1
Increase in levels of liver proteins	1
Joint pain	1
Muscle pain	1
Accidental overdose of emicizumab*	1

*Accidental overdose of emicizumab is a medication error due to accidentally taking emicizumab in a quantity that is higher than the assigned dose. This is a special situation associated with emicizumab, not a side effect in itself. No side effects resulted from this medication error.

Common side effects of emicizumab

A side effect is considered 'common' if it is seen in more than 5% of people (1 out of 20). Injection site reactions were the only **common side effect** that the study doctors believed could be related to emicizumab.

Serious side effects related to emicizumab

A side effect is considered 'serious' if it is life-threatening, needs hospital care, causes lasting problems and severe limitation of activity, or causes death. No one in the study had a **serious side effect** that the study doctor believed could be related to emicizumab.

Question 2: Did anyone have a blood clot while receiving emicizumab?

When a blood clot forms and blocks a blood vessel, this is called a '**thrombotic event**'. Very small – also called microscopic – blood clots are called '**thrombotic microangiopathies**' or **TMAs.**

In a previous study of emicizumab in people with inhibitors against factor eight, two people had a thrombotic event and three people had a TMA. These five people were also taking a bypassing agent called '**activated prothrombin complex concentrate**' to treat bleeds. When the clotting events happened, this bypassing agent had been taken multiple times to reach a certain dose level and kept at that dose for more than one day. After these events, the study sponsors gave instructions about how to use this bypassing agent more safely in people taking emicizumab.

Study doctors wanted to check if anyone had these clotting problems in this study. One person in this study had blood clotting in a haemorrhoid (sometimes called a '**thrombosed haemorrhoid**', a type of thrombotic event). The study doctors believed this blood clotting was not related to emicizumab and was instead linked to conditions other than haemophilia A. The blood clot was not serious, the person recovered and did not stop taking emicizumab. No one in this study had a microscopic blood clot (TMA).

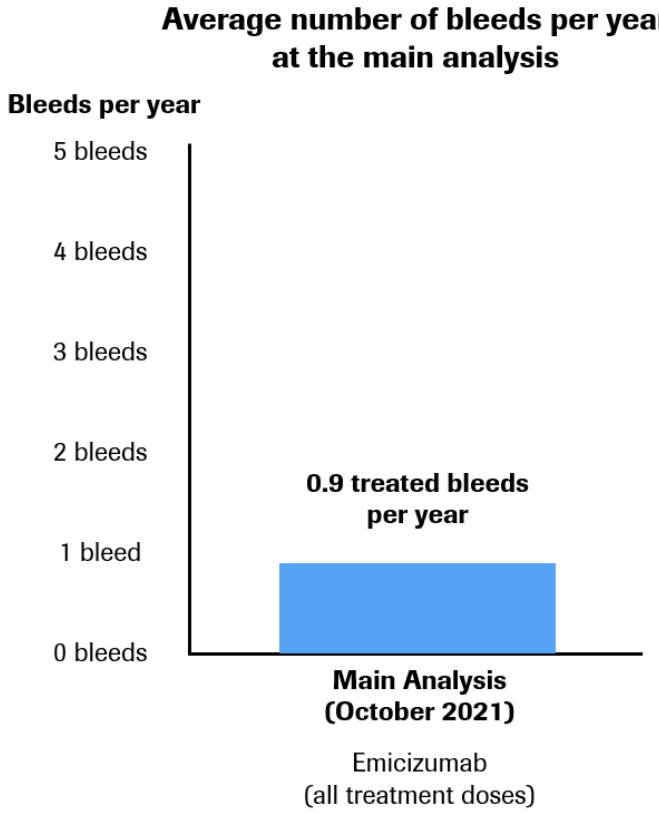
5. What other results were reported in this study?

Question 3: How many bleeds did people with moderate or mild haemophilia A without factor eight inhibitors have when given emicizumab?

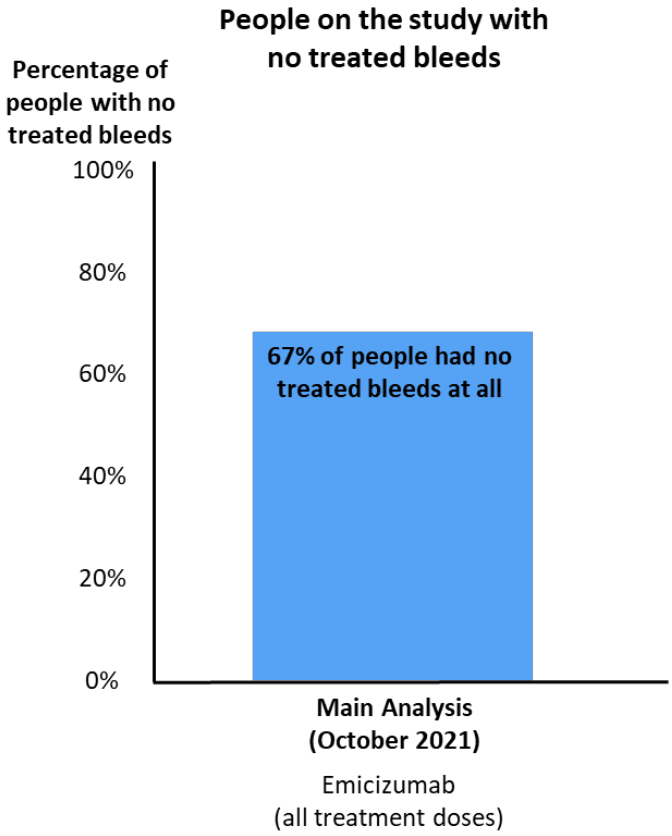
If a person had a bleed while taking part in the study, they could treat the bleed with another type of medication, such as factor eight replacement. Bleeds that are treated in this way are called '**treated bleeds**'.

Study doctors looked at how many treated bleeds people had, on average, over the course of the study, when taking emicizumab to prevent bleeding. Doctors then used the numbers of treated bleeds people had during this time and estimated how many treated bleeds that person would be likely to have over the course of an average year.

People had, on average, less than one treated bleed per year (0.9 bleeds per year reported at the main analysis).



Study doctors also looked at how many people in the study did not have any treated bleeds while receiving emicizumab. At the time of the interim analysis (April 2021), people had been part of the study for an average of 27.5 weeks. At that time, 57 people out of the 71 people receiving emicizumab (80%) had no treated bleeds at all. Some people who had no treated bleeds at the time of the interim analysis had a treated bleed later on. At the time of the main analysis (October 2021), people had been part of the study for a longer average duration of 55.6 weeks. At that time, 48 people out of the 72 people receiving emicizumab (67%) had no treated bleeds at all.



This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see section 8).

6. How does this study help research?

The results presented here are helping doctors to learn more about the effect of emicizumab in people with moderate or mild haemophilia A without inhibitors against factor eight.

The results show that around 2 in 10 people receiving emicizumab in the study had a side effect related to emicizumab treatment. These side effects were mostly injection site reactions and considered mild. One person in this study had blood clotting in a haemorrhoid (thrombotic event). The study doctors believed this blood clotting was not related to emicizumab.

The results show that people receiving emicizumab who had mild or moderate haemophilia A without inhibitors against factor eight experienced, on average, less than one treated bleed per year.

No single study can tell us everything about the risks and benefits of a medicine. It takes many people taking part in several studies to find out what we need to know. This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

7. Are there plans for other studies?

Other studies looking at emicizumab treatment are taking place, and further studies are planned.

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/NCT04158648
- https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(22)00377-5/fulltext

If you would like to find out more about the results of this study, the full title of the relevant scientific abstract for the interim analysis results (April 2021) is "Emicizumab Prophylaxis in Persons with Mild or Moderate Hemophilia A: Results from the Interim Analysis of the HAVEN 6 Study". The authors of the scientific abstract are: Claude Négrier, Johnny Mahlangu, Michaela Lehle, Pratima Chowdary, Olivier Catalani, and others. It is published in the '*Blood*' journal, volume number 138 (Supplement 1), on page 343.

The full title of the relevant scientific abstract for the main analysis results (October 2021) is "Emicizumab Prophylaxis for the Treatment of People with Moderate or Mild Hemophilia A without Factor VIII Inhibitors: Results from the Primary Analysis of the HAVEN 6 Study". The authors of the scientific abstract are: Cedric Hermans, Claude Négrier, Michaela Lehle, Pratima Chowdary, Olivier Catalani, and others. It is published in the '*Research and Practice in Thrombosis and Haemostasis*' journal, volume number 6 (Supplement 1), on page 78.

The full title of the relevant scientific paper for the main analysis results (October 2021) is "Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study". The authors of the scientific paper are: Claude Négrier, Johnny Mahlangu, Michaela Lehle, Pratima Chowdary, Olivier Catalani,

and others. The paper is published online in '*Lancet Haematology*', doi:10.1016/S2352-3026(22)00377-5.

Who can I contact if I have questions about this study?

If you took part in this study and have any questions about the results:

- speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- speak to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd, who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is "A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Emicizumab in Patients With Mild or Moderate Hemophilia A Without FVIII Inhibitors (HAVEN 6)".

The study is known as 'HAVEN 6'.

- The protocol number for this study is: BO41423.
- The ClinicalTrials.gov identifier for this study is: NCT04158648.
- The EudraCT number for this study is: 2019-002179-32.

9. Infographic summary

A study to look at the side effects of taking emicizumab in people with moderate or mild haemophilia A without inhibitors against factor eight – and how well emicizumab prevented bleeding

This is a summary of the results of a study, written for the adolescent and adult participants, general public and the caregivers of the children that took part. This study started in February 2020 and is expected to end in April 2023. This summary focuses on the results from the main analysis carried out in October 2021.

Why is this study being done?

People with haemophilia A, a rare inherited bleeding disorder, have a condition where their blood cannot clot properly and they are likely to have many bleeds. People with haemophilia A can have severe, moderate, or mild forms of haemophilia A.

A medicine called emicizumab has been shown to help prevent bleeding in people with **severe haemophilia A**.

Doctors are doing this study to look at the side effects of **emicizumab** in people with **moderate or mild haemophilia A** without **inhibitors against factor eight**, and whether emicizumab can prevent bleeding in these people.

Who is taking part in this study?

This study is taking place at: **22** centres across the world in **10** countries around the world

72 people had taken part: 69 males and 3 females.
51 people had **moderate haemophilia A**.
21 people had **mild haemophilia A**.

The age of people in the study ranged from **2** to **71 years**.

What is happening during this study?

After receiving the **loading dose** (emicizumab 3 mg/kg once a week) for the first four weeks of the study, people had a choice of which **maintenance dose** of emicizumab they received.

Emicizumab 1.5 mg/kg **once every week** OR Emicizumab 3 mg/kg **once every two weeks** OR Emicizumab 6 mg/kg **once every four weeks**

- Doctors looked at how many **side effects** people with moderate or mild haemophilia A had while receiving emicizumab.
- Doctors looked at how many **treated bleeds** people had, on average, over the course of a year.

What side effects related to the study medicine were reported in this study?

Side effects related to emicizumab

Around **2 in every 10 people (21%)** had a side effect related to emicizumab.

A side effect is considered 'common' if it is seen in more than 5% of people (1 out of 20).
Injection site reaction (redness of the skin where the injection was given) was the only 'common' side effect related to emicizumab – the majority of symptoms were mild.

There were **no serious side effects related to emicizumab**.

Did anyone have a blood clot while receiving emicizumab?

One person in this study had blood clotting in a haemorrhoid (sometimes called '**thrombosed haemorrhoid**', a type of **thrombotic event**). The person recovered and study doctors believed this blood clot was **not related to emicizumab**.

What other results were reported in this study?

People had, on average, **less than one treated bleed per year**.

0.9 bleeds per year were reported.

The majority of people had **no treated bleeds** at all.

67% had no treated bleeds.

What does this study tell us?

The results show that around 2 in 10 people receiving emicizumab in this study had a side effect related to emicizumab treatment, mostly mild injection site reactions. One person had blood clotting in a haemorrhoid that study doctors believed was not related to emicizumab. The results also show that people receiving emicizumab in this study had, on average, less than one treated bleed per year.

This study is known as 'HAVEN 6' (NCT04158648) and was organised and paid for by F. Hoffmann-La Roche Ltd. ¦ M-XX-00012536 ¦ Date of preparation: February 2023.

For the definition of '**loading dose**', '**maintenance dose**', '**mild haemophilia A**', '**moderate haemophilia A**', '**inhibitors against factor eight**', '**severe haemophilia A**', '**side effects**', '**serious side effects**', '**thrombotic event**', '**thrombosed haemorrhoid**' and '**treated bleeds**', please see the glossary section of the layperson summary.

10 Glossary

Activated prothrombin complex concentrate	A type of bypassing agent to help the blood clot in people who have inhibitors against factor eight.
Clinical trial	When researchers give a group of people a medicine to find out more information about how the medicine works, if it helps to improve people's condition, and if it causes any side effects. The researchers regularly follow up with the people taking the medicine and perform medical tests.
Common side effect or adverse event	A side effect or adverse event that is seen in more than 5% of people (1 out of 20).
Gene	Genes are units of DNA inherited from our parents that contain all the information needed to make people who they are – from the colour of someone's eyes to their blood type. DNA is the code that carries the instructions to build all known living organisms, from bacteria to humans.
Inherited	Passed on from one generation to the next through certain genes.
Inhibitors against factor eight	Antibodies produced as a reaction by the body's immune system in response to treatment with replacement factor eight. Inhibitors against factor eight can stop replacement factor eight treatment from working to prevent bleeds. Inhibitors against factor eight often develop at a young age when children are first treated with replacement factor eight.
Injection site reaction	Redness, pain or swelling of the skin at the site where an injection was given.
IV injection	Intravenous injection. An injection into a vein.
Loading dose	An initial higher dose of a medicine that may be given at the beginning of a course of treatment to increase levels of the medicine in the blood quickly before dropping to a lower maintenance dose of that same medicine.
Maintenance dose	The amount of medication given to maintain a level of the medicine in the blood that is expected to be effective and cause minimal side effects.
Mild haemophilia A	People with haemophilia A have little to no activity of a protein in the blood called 'clotting factor eight'. Mild haemophilia A means that people have a factor eight activity of between 5% and 40% of the level observed in someone without haemophilia A.

Mild side effect or adverse event	A side effect or adverse event that causes mild discomfort, lasts for less than 2 days, and does not need any treatment.
Moderate haemophilia A	People with haemophilia A have little to no activity of a protein in the blood called 'clotting factor eight'. Moderate haemophilia A means that people have a factor eight activity between 1% and 5% of the level observed in someone without haemophilia A.
Moderate side effect or adverse event	A side effect or adverse event that causes mild to moderate limitation in activity, may cause the person to need some assistance, and needs little or no treatment.
On-demand treatment	Treatment given immediately after a bleed has happened to help the bleeding stop.
Open label	A clinical trial where both the researchers and the people taking part know which of the study medicines people are taking.
Phase 3 trial	A clinical trial to collect more information on how effective and safe the new medicine is. If a new drug is shown to be effective and has a favourable safety profile in a Phase 3 study, the results can be used to gain approval from health authorities in different countries to make the drug available to people.
Prophylactic treatment	Treatment given on a regular basis. In people with haemophilia A, this is given to prevent bleeding and subsequent joint and muscle damage.
Protein	A long chain of very small units in our body called amino acids that are organised into both simple and complex structures, and form almost everything in a living organism, from hair and skin to enzymes and antibodies. Information on how to build proteins is found in the genes.
Replacement factor eight	Factor eight treatment given to replace the missing or inactive factor eight in people with haemophilia A. This can be taken from human blood donations, or artificially created in a laboratory.
Serious side effect or adverse event	A side effect or adverse event that is life-threatening, needs hospital care, causes lasting problems and severe limitation of activity, or causes death.
Severe haemophilia A	People with haemophilia A have little to no activity of a protein in the blood called 'clotting factor eight'. Severe haemophilia A means that people have a factor eight activity less than 1% of the level observed in someone without haemophilia A.

Side effect	An unwanted medical effect that happens when taking a medicine and is believed by doctors to be related to the medicine.
Subcutaneous injection	An injection under the skin.
Thrombotic event	An event that occurs when a blood clot forms and blocks a blood vessel.
Thrombosed haemorrhoid	A haemorrhoid is a swollen vein located around the anus or lower rectum. A thrombosed haemorrhoid is when a blood clot becomes trapped inside a haemorrhoid.
Thrombotic microangiopathy (TMA)	Formation of a very small – microscopic – blood clot.
Treated bleed	A bleed treated with another type of medication, such as factor eight replacement.
X chromosome	One of two sex-determining chromosomes in humans, of which males have one, and females have two.