

## Clinical Trial Results – Layperson Summary

### A study looking at whether emicizumab can prevent bleeding in people aged 12 years and older with haemophilia A in the Asia-Pacific region – and whether there are any side effects of taking emicizumab

See the end of the summary for the full title of this study, and a hyperlinked **[glossary](#)** of medical terms.

#### About this summary

This is a summary of the results of a **clinical trial** (called a ‘study’ in this document) – written for:

- members of the public, and
- people who took part in the study.

This study started in April 2018 and is expected to end in November 2022. This summary focuses on the published results when the main analysis took place (up until June 2019). 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 treatment decisions.

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#### Thank you to the people who took part in this study

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

## 1. General information about this study

### What is haemophilia A?

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Haemophilia A is a rare **inherited** blood disorder caused by an abnormal **gene**. It mostly affects men and boys – less than 1% of people with severe 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.

### How is haemophilia A treated?

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Historically, standard treatment for people with haemophilia A was 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.

Around one in five people with haemophilia A develop what are called **inhibitors against factor eight**. This happens because the replacement factor eight is unfamiliar to the body, so the body develops inhibitors to destroy it. This stops replacement factor eight treatment from working, which makes it more difficult to prevent a bleed from happening.

Due to this, people who develop these inhibitors have only a few treatment options. One treatment option is called **immune tolerance induction** or ITI, whereby, factor eight is administered in small doses to begin with and then the doses are gradually increased. The person’s immune system eventually learns to tolerate factor eight and stops developing inhibitors against it.

Other options include treatments called '**bypassing agents**'. Instead of replacing the missing or inactive factor eight, they go around (or bypass) it to help the blood clot. Bypassing agents are also given as an injection into a vein. Preventative (prophylactic) bypassing agents have limitations and do not always protect against bleeds in all people with haemophilia A with inhibitors against factor eight. Some people taking part in this study have **inhibitors against factor eight**.

## **Why is this study being done?**

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This study is being done to see whether a new medicine – emicizumab – can prevent bleeding in people with haemophilia A, with or without inhibitors against factor eight, who are aged 12 years or older in the Asia–Pacific region. This study also looks at whether there are any side effects of taking emicizumab (for more information, please read the section entitled “What do doctors want to find out?”).

## **What is the study medicine?**

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A medicine called 'emicizumab' is the focus of this study.

- You say this as 'em – me – sih – zuh – mab'.
- Emicizumab works by acting on proteins found in the blood to replace the function of the missing or inactive factor eight – this leads to blood clotting.
- The proteins that emicizumab acts on are other clotting factors, not factor eight itself.
- Emicizumab improves the ability of the blood to make clots and 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. This is different from replacement factor eight treatment, which is given as an injection into a vein.

## **What do doctors want to find out?**

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Doctors are doing this study to see:

- If emicizumab can prevent bleeding in people with haemophilia A, with or without inhibitors against factor eight, compared with no preventative treatment (meaning people didn't take emicizumab or any other preventative treatment). The participants who were not receiving preventative treatment prior to joining the study continued to receive standard-of-care treatments on an 'on-demand' basis for the treatment of breakthrough bleeds during the study - see section 4 “What were the results from the main analysis of this study?”.
- How safe emicizumab is when given to people with haemophilia A, with or without inhibitors against factor eight, once every week or once every 4 weeks. The doctors will check how many people have side effects when taking emicizumab during this study and what these side effects are (see section 5 “What side effects related to the study medicine were reported in the main analysis of this study?”).

## What kind of study is this?

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Emicizumab had previously been tested in smaller **Phase 1** and **Phase 2** studies. This was a larger **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 to people with haemophilia A. Please see the glossary for full explanations of Phase 1, Phase 2 and Phase 3 studies.

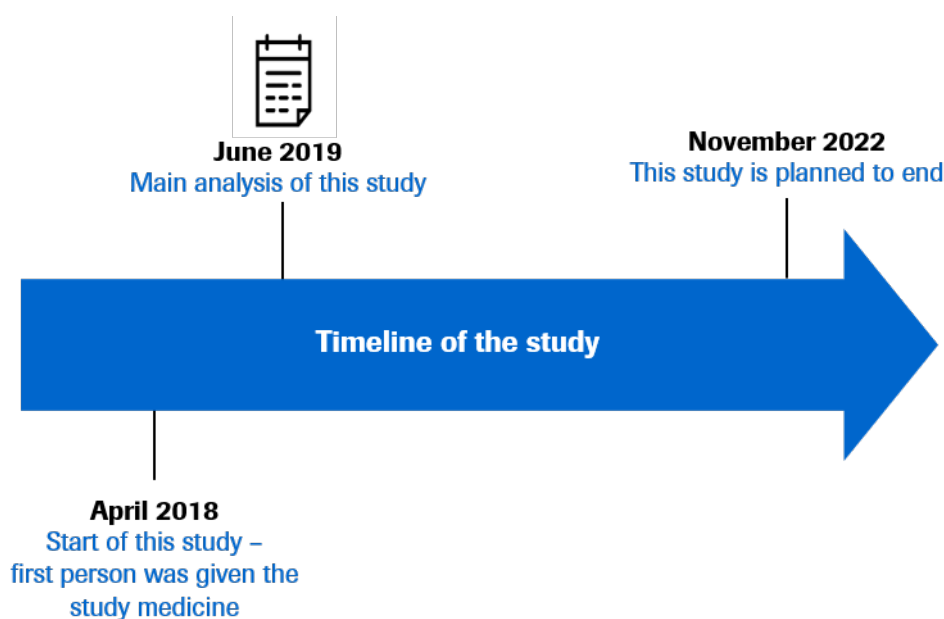
This study was '**randomised**'. This means that whether a person would receive emicizumab or no preventative treatment was decided by chance, like rolling dice.

This was an '**open-label**' study. This means that both the doctors and the people taking part in this study knew what treatment the people were receiving.

## When and where is this study taking place?

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This study started in April 2018 and is expected to end in November 2022. This summary focuses on the results of the main analysis, up until June 2019 – over one year after the start of the study. At the time of writing this summary, the study is still ongoing – study doctors are still collecting information and people taking part in the study are still being monitored.



The calendar symbol on the timeline (📅) shows when the results in this summary were collected – June 2019.

The study is taking place at 13 study centres across the Asia–Pacific region. The following map shows the countries where this study is taking place.



## 2. Who is taking part in this study?

In this study, 70 people with haemophilia A, with or without inhibitors against factor eight, are taking part. They are all males, aged 12 years or older.

People can take part in this study if they:

- are aged 12 years or older
- have had a diagnosis of severe congenital haemophilia A or haemophilia A with factor eight inhibitors
- have been taking ‘on-demand’ replacement factor eight or a bypassing agent to treat their haemophilia A, for at least 24 weeks before the start of the study.

People cannot take part in this study if they:

- have diseases or conditions other than haemophilia A that might have increased their risk of bleeding
- have taken emicizumab in a previous study
- have planned to have a surgery during this study (not including simple surgeries like having a tooth removed).

## 3. What is happening during this study?

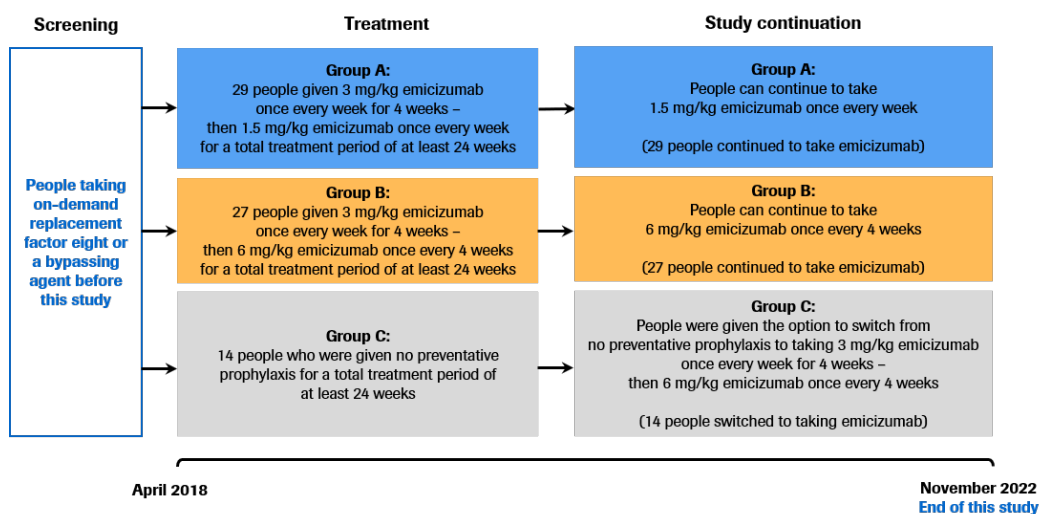
People who were taking on-demand replacement factor eight or bypassing agents before the start of this study were assigned by chance (**randomised**) to one of three groups – Group A, Group B or Group C.

During this study, people were given emicizumab as an injection underneath the skin.

The treatment groups are:

- **Group A** – to quickly increase the amount of emicizumab in their blood, these people were first given 3 mg/kg emicizumab (meaning three milligrams of emicizumab for every one kilogram of body weight) once every week for 4 weeks. These are called the '**loading doses**'. After 4 weeks, they started taking 1.5 mg/kg emicizumab once every week for a total treatment time of at least 24 weeks. These are called the '**maintenance doses**'.
- **Group B** – as in Group A, these people were first given loading doses of 3 mg/kg emicizumab once every week for 4 weeks. After 4 weeks, they started taking maintenance doses of 6 mg/kg emicizumab once every 4 weeks for a total treatment time of at least 24 weeks.
- **Group C** – these people did not receive emicizumab (or any preventative treatment) for the first 24 weeks of this study. After the main analysis (after 24 weeks), the people in Group C could start taking emicizumab if they wanted to. If they decided to take emicizumab, these people were first given loading doses of 3 mg/kg emicizumab once every week for 4 weeks. After four weeks, they started taking maintenance doses of 6 mg/kg emicizumab once every 4 weeks for at least 24 weeks.

Everyone in the study could receive 'on-demand' replacement factor eight or a bypassing agent called recombinant activated factor seven to treat a bleed. People were told not to use another type of bypassing agent called activated prothrombin complex concentrate, but if they had to use it because recombinant activated factor seven was not available, only the smallest dose should be taken at first. This is because four people in the HAVEN 1 clinical trial experienced a serious side effect related to emicizumab when also taking activated prothrombin complex concentrate at the same time at a certain dose level. After the study had finished, study sponsors gave instructions how to use this bypassing agent more safely in people taking emicizumab, and no more serious side effects were reported up to the final analysis.



After the main analysis at 24 weeks, people taking part in the study could continue to take emicizumab or change to a different treatment if they preferred. Of those who initially did not receive any preventative treatment in Group C, all 14 people chose to begin treatment with emicizumab after 24 weeks.

#### 4. What were the results from the main analysis of this study?

**Question 1:** How many bleeds did people have when given emicizumab once every week or once every 4 weeks compared with people who had no preventative treatment (on-demand treatment only)?

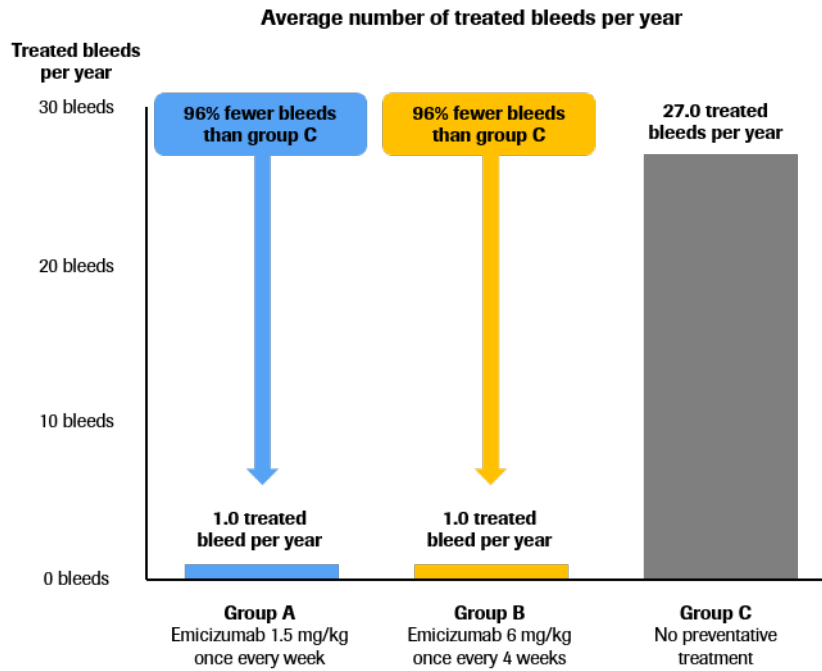
As noted above, if a person had a bleed while taking part in the study, they could treat the bleed with replacement factor eight or a bypassing agent called recombinant activated factor seven. Bleeds treated in this way are called '**treated bleeds**'.

Doctors looked at how many treated bleeds people had on average over the course of a year, when taking emicizumab to prevent bleeding. This has been compared with how many treated bleeds people in Group C had on average over the course of a year, when they were taking no preventative treatment (on-demand treatment only). At the time of the main analysis, some people in this study had not been monitored for a full year. If this was the case, doctors used the numbers of treated bleeds people had during the time they were monitored and estimated how many treated bleeds that person could potentially have over the course of a year.

People in Group A, who were given maintenance emicizumab once every week, had on average one treated bleed per year. Two thirds of them (19 out of 29 people, 65.5%) had no treated bleeds. Most of the people in Group A (93.1%) had severe haemophilia A.

People in Group B, who were given emicizumab once every 4 weeks, had on average one treated bleed per year. Over one half of them (15 out of 27 people, 55.6%) had no treated bleeds. All of the people in Group B (100%) had severe haemophilia A.

People in Group C, who were not receiving preventative treatment for the first 24 weeks, had on average 27 treated bleeds per year. Most of the people in Group C (13 out of 14, 92.9%) had at least one treated bleed and most (92.9%) had severe haemophilia A.



## 5. What side effects related to the study medicine were reported in the main analysis of this study?

### Question 2: How many people had side effects 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. Unrelated side effects are not listed in this document.
- Not all of the people in this study had side effects.
- 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.

People from Groups A, B and C who received emicizumab treatment are included in the main safety results. For Group C, all participants chose to take emicizumab after at least 24 weeks on the study. The safety results for a total of 70 people are available and all results are included in this section.

### Serious side effects

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.



Up to the time of the main analysis, none of the people taking part in the study had experienced a **serious side effect** related to emicizumab treatment.

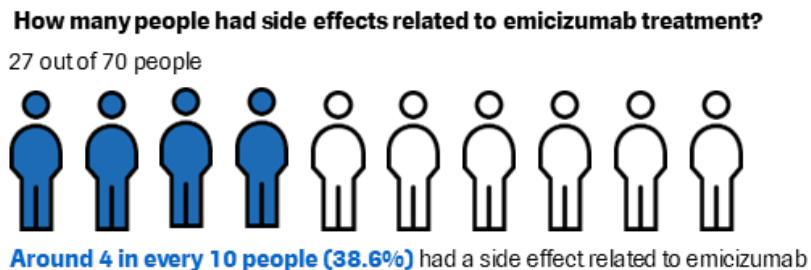
### Common side effects

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Side effects are considered '**common**' if they are seen in more than 5% of people (1 out of 20) in all treatment groups.

Up to the time of the main analysis, approximately four in ten people (38.6%) across Groups A, B and C had a common side effect related to emicizumab treatment that was considered mild or moderate in severity and **not** considered serious.

A side effect is considered '**mild**' if it causes mild discomfort, lasts less than two 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 these side effects were redness of the skin where the injection was given. This is called an '**injection-site reaction**'. In most people who had injection-site reactions, symptoms were considered mild.

Redness of the skin where the injection was given, and an increase in proteins from the liver found in the blood were the only 'common' side effects related to emicizumab seen up to the time of the main analysis.

## Other side effects

This table lists all groups of side effects up to the time of the main analysis that the doctors believed to be related to emicizumab. It also shows the number of people in Groups A, B and C who had each of these side effects.

Side effect	Group A (29 people)	Group B (27 people)	Group C (14 people)	All groups (70 people)
<b>Changes in protein levels</b>	7	7	3	17
<b>General effects (e.g., injection-site reaction)</b>	4	6	1	11
<b>Nervous system problems (e.g., sore head)</b>	2	1	1	4
<b>Skin problems (e.g., itchy skin)</b>	1	2	0	3
<b>Blood problems (e.g., low blood count)</b>	1	1	0	2
<b>Heart problems (e.g., fast heartbeat)</b>	1	1	0	2
<b>Stomach problems (e.g., feeling sick)</b>	1	1	0	2
<b>High blood pressure</b>	0	2	0	2
<b>Ringing in the ears (tinnitus)</b>	0	0	1	1
<b>Liver not working properly</b>	0	0	1	1
<b>Immune system not working properly</b>	1	0	0	1
<b>Muscular problems or pain</b>	0	0	1	1
<b>Urine problems</b>	1	0	0	1
<b>Breathing problems</b>	1	0	0	1

The side effects that occurred in people from Arm C, had already switched to emicizumab after at least 24 weeks on the study. You can find information about other side effects that were not related to emicizumab (not shown here) on the websites listed at the end of this summary (see section 8 “Where can I find more information?”).

## 6. How has this study helped research?

The results presented here are from a single study of a total of 70 people aged 12 years and older with haemophilia A, with or without inhibitors against factor eight, in the Asia–Pacific region. The results are helping doctors to learn more about the effect of emicizumab in people with haemophilia A, with or without inhibitors against factor eight, from the Asia–Pacific region.

Other studies have shown that emicizumab can prevent bleeding in adults and children with haemophilia A, with or without inhibitors against factor eight, when emicizumab is given once every week, once every 2 weeks, or once every 4 weeks.

The results from this study show that, in people with haemophilia A, with or without inhibitors against factor eight, emicizumab given once every week or once every 4 weeks better prevented bleeding than no preventative (on-demand) treatment. The results also show that emicizumab was well tolerated in most people enrolled in the study as less than four in ten people (38.6%) had a side effect related to emicizumab treatment. None of these side effects were serious.

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 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 website listed below:

- <https://clinicaltrials.gov/ct2/show/NCT03315455>

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: “A randomised study of prophylactic emicizumab in people with haemophilia A in the Asia–Pacific region (HAVEN 5)”. The authors of the scientific paper are: Shujie Wang, Xuefeng Wang, Jing Sun, Ampaiwan Chuansumrit, Jianfeng Zhou and others. The paper is published in the journal *Research and Practice in Thrombosis and Haemostasis*.

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

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If you have any further questions after reading this summary:

- visit the ForPatients platform and fill out the contact form <https://forpatients.roche.com/en/About.html>
- or, contact a representative at the local Roche office in your country.

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?**

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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**

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The full title of this study is: “A randomised study of prophylactic emicizumab in persons with haemophilia A in the Asia–Pacific region (HAVEN 5)”.

The study is known as ‘HAVEN 5’.

- The protocol number for this study is: YO39309.
- The ClinicalTrials.gov identifier for this study is: NCT03315455.

## 9. Infographic summary

Roche

### A study looking at whether emicizumab can prevent bleeding in people aged 12 years and older with haemophilia A in the Asia-Pacific region – and whether there are any side effects of taking emicizumab



This is a summary of the results of a study, written for the general public and the people taking part. This study started in April 2018 and is expected to end in November 2022. This summary focuses on the published results up until June 2019, when the main analysis took place.

#### Why was this study done?

People with haemophilia A, a rare inherited bleeding disorder, have little to no activity of a protein called 'clotting factor eight'. This means their blood cannot clot properly and they are likely to have many bleeds.

Historically, standard treatment to improve the ability of the blood to clot was to deliver active 'replacement factor eight' as an injection into a vein.

People with haemophilia A can develop inhibitors against factor eight, which can stop the replacement factor eight treatment from working.



A medicine called **emicizumab** was the focus of this study. Doctors did this study to see if emicizumab given once every week or once every 4 weeks can prevent bleeding in people with haemophilia A, with or without inhibitors against factor eight, and to look at whether there are any side effects of taking emicizumab.

#### Who took part in this study?

This study took place at:



13

centres across the Asia-Pacific Region



3

countries across the region



people with haemophilia A took part.

They were aged **12 years** or older and were all male.

#### What happened in this study?

- Those taking on-demand replacement factor eight or bypassing agents before the start of this study were assigned by chance to one of three treatment groups – Group A, Group B, or Group C.

##### Group A

29 people



Emicizumab 3 mg/kg once every week for 4 weeks

then ↓



**Emicizumab 1.5 mg/kg once every week** for at least 24 weeks

##### Group B

27 people



Emicizumab 3 mg/kg once every week for 4 weeks

then ↓



**Emicizumab 6 mg/kg once every four weeks** for at least 24 weeks

##### Group C

14 people



**No preventative treatment** for at least 24 weeks, then could choose to receive



Emicizumab 3 mg/kg once every week for 4 weeks

then ↓

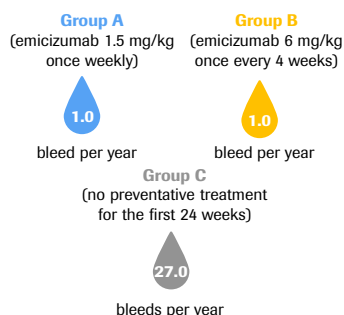


**Emicizumab 6 mg/kg once every four weeks** for at least 24 weeks

- If a person had a bleed while taking part in the study, they could treat the bleed with replacement factor eight or a bypassing agent called recombinant activated factor seven. Bleeds treated in this way are called 'treated bleeds'.
- Doctors looked at how many treated bleeds people had, on average, over the course of a year when taking emicizumab to prevent bleeding, compared with how many treated bleeds people in Group C had over the course of a year when they were taking no preventative treatment.

#### What were the results from the main analysis of this study?

People in **Group A and B** who were taking emicizumab once every week and once every four weeks, respectively, had **96% fewer treated bleeds** than people in Group C who received no preventative treatment for the first 24 weeks.



#### What side effects related to the study medicine were reported in the main analysis of this study?

The side effects reported below are those that the study doctors believed to be related to emicizumab treatment.

##### Common side effects



Around **4 in every 10 people (38.6%)** had a side effect related to emicizumab.

Side effects are considered '**common**' if they are seen in **more than 5% of people (1 out of 20)** in all treatment groups. Redness of the skin where the injection was given (called an '**injection-site reaction**') and an increase in **proteins** from the liver found in the blood were the only 'common' side effects related to emicizumab – the majority of **injection-site reaction** symptoms were mild.

##### Serious side effects

Up to the time of the main analysis, **none of the people** taking part in the study experienced a **serious side effect** related to emicizumab treatment.

#### What did this study tell us?

Emicizumab given once every week or once every 4 weeks better prevented bleeding than no preventative (on-demand) treatment. The results also show that emicizumab was well tolerated in most people enrolled in the study as less than four in ten people (38.6%) had a side effect related to emicizumab treatment. None of these side effects were serious.

This study is known as 'HAVEN 5' (NCT03315455) and was organised and paid for by F. Hoffmann-La Roche Ltd. M-XX-00012639 Date of preparation: March 2023.

For the definition of 'bypassing agents', 'inhibitors against factor eight', 'replacement factor eight', 'side effects' and 'serious side effects', please see the glossary section of the layperson summary.

## 10. Glossary

Bypassing agents	Treatment given to people with haemophilia with inhibitors against factor eight. Instead of replacing the missing or inactive factor eight, bypassing agents go around (or bypass) it to help the blood clot.
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	A side effect that is seen in more than 5% of the people (1 out of 20).
DNA	DNA is the code that forms the building blocks of all known living organisms, from bacteria to humans. The DNA in our body carries the instructions to build us, and is the material that makes up our genes.
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.
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.
Immune tolerance induction	A treatment for people with haemophilia A with inhibitors against factor eight, where factor eight is administered in small doses to begin with and then the doses are gradually increased. The person's immune system eventually learns to tolerate factor eight and stops developing inhibitors against it.
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 offers acceptable bleed protection.
Mild side effect	A side effect that causes mild discomfort, lasts for less than two days, and does not need any treatment.
Moderate side effect	A side effect 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 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 1 study	One of the first clinical trials investigating a new medicine. Study doctors give the new medicine to a small number of people, to look at how it affects them and find out more about the medicine.
Phase 2 study	A clinical trial to look at how effective a new medicine is in people with the disease or condition being studied, and to determine what the side effects of the new medicine are. Phase 2 studies involve more people and usually last longer than Phase 1 studies.
Phase 3 study	A clinical trial to further evaluate how effective and safe the new medicine is, usually involving more people than Phase 1 and 2 trials. Phase 3 trials may also compare a new medicine with an existing treatment option to show which medicine works better (the new medicine or the old one), what the side effects of the new medicine are, and how the new treatment affects people's quality of life.
Prophylactic treatment	Treatment given on a regular basis 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.
Randomised	A trial in which people are split into groups at random. This is usually done by a computer. Usually, each group will be given a different type of treatment.
Replacement factor eight	Factor eight treatment given to replace the missing or inactive factor eight in people with haemophilia A. This

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	can be taken from human blood donations, or artificially created in a laboratory.
Safety profile	An overview of the characteristics of the medicine, including how it works, what it does, and any side effects.
Serious side effect	A side effect that is life-threatening, needs hospital care, causes lasting problems and severe limitation of activity, or causes death.
Side effect	An unwanted medical effect that is caused by taking a medicine. Side effects can be positive or negative.
Treated bleed	A bleed treated with replacement factor eight or bypassing agents.

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