# Clinical Trial Results – Layperson Summary

## A study looking at whether emicizumab can prevent bleeding in people aged 12 years and older with haemophilia A when given once every 4 weeks – and whether there are any side effects of taking emicizumab

See the end of the summary for the full title of the study, and a 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.

The study started in January 2017 and is expected to end in June 2022. This summary includes the results up until December 2017 when the main analysis took place. 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 are taking part in this study

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

# 1. General information about this study

## Why is this study being done?

Haemophilia A is a rare **inherited** bleeding 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.

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.

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.

People who develop these inhibitors have only a few treatment options. These options are 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.

Emicizumab is another type of medicine for haemophilia A. It has been shown in previous studies that emicizumab given once every week or once every 2 weeks helps to prevent bleeding in people with haemophilia A. It is effective in people with inhibitors against factor eight and people without inhibitors against factor eight.

This study is being done to see whether emicizumab given as a larger amount once every 4 weeks can help prevent bleeding in people with haemophilia A. This could help to reduce **treatment burden**, by requiring less frequent injections (once every 4 weeks instead of once every week or once every 2 weeks). This study is also looking at whether there are any **side effects** of taking a larger amount of emicizumab once every 4 weeks.

## What is the study medicine?

A medicine called 'emicizumab' (HEMLIBRA®) is the focus of this study.

- You say this as 'em – me – sih – zuh – mab'.
- Emicizumab works by acting on clotting factor proteins found in the blood (not factor eight) to replace the function of the missing or inactive factor eight.
- This 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 than replacement factor eight treatment, which is given as an injection into a vein.

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

## What do doctors want to find out?

Doctors have shown in previous studies that emicizumab can prevent bleeding when given to people with haemophilia A once every week or once every 2 weeks.

Emicizumab takes quite a long time to leave the body, so it may be possible for patients to be treated less often than once every week or once every 2 weeks without reducing the effect.

Doctors want to find out whether emicizumab can prevent bleeding when given as a larger amount once every 4 weeks as well as it does when given as a smaller amount once every week or once every 2 weeks (see section 4 "What were the results from the main analysis of this study?").

Doctors also want to find out how safe emicizumab is when given as a larger amount once every 4 weeks - by checking how many people have side effects when taking emicizumab during this study (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?

Emicizumab had previously been tested in smaller **Phase 1** and **Phase 2** studies. This is 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.

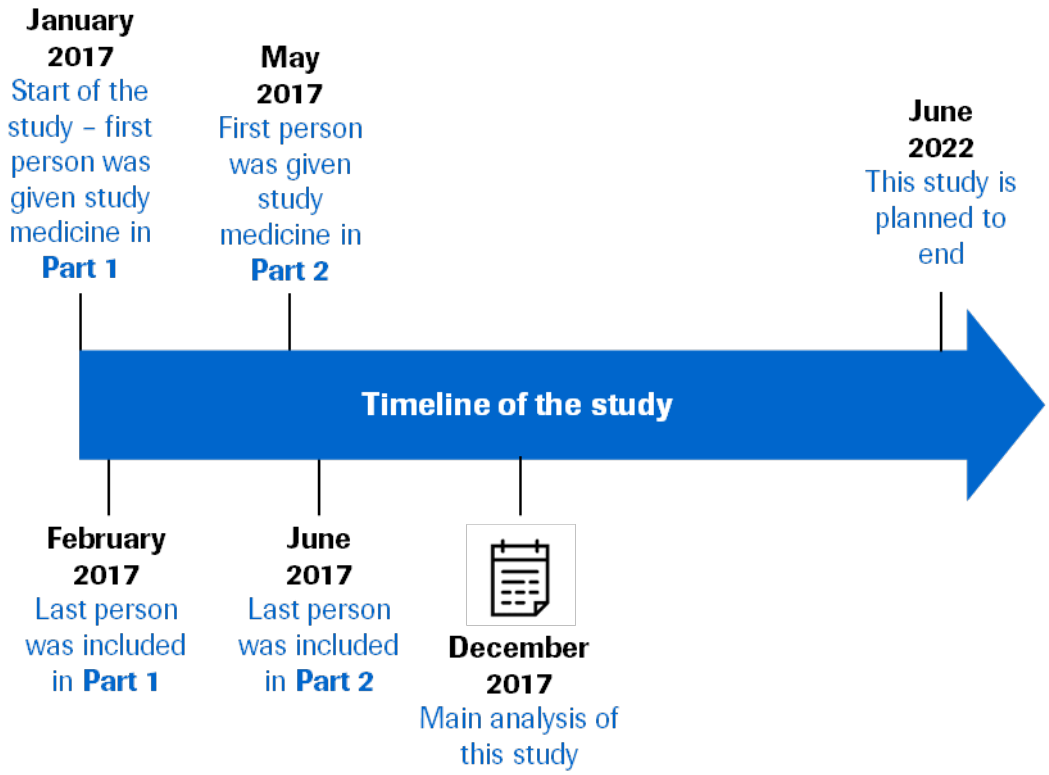
Please see the glossary for full explanations of Phase 1, Phase 2, and Phase 3 studies. At the time this study started, other Phase 3 studies with emicizumab were ongoing. These studies provided results on emicizumab given once every week or once every 2 weeks.

This is an **'open label'** study. This means that both the doctors and the people taking part in the study know how they are being treated. In this study, all individuals taking part received emicizumab once every 4 weeks.

The study is split into two parts – Part 1 and Part 2 (see section 3 "What is happening during this study?") This summary includes the key results from the main analysis of Part 2.

## When and where is this study taking place?

The study started in January 2017 and is expected to end in June 2022. This summary includes the results of the main analysis, up until December 2017 – nearly a 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 picture (📋) shows when the results in this summary were collected – December 2017.

Part 1 of the study is taking place at three study centres, across two countries.

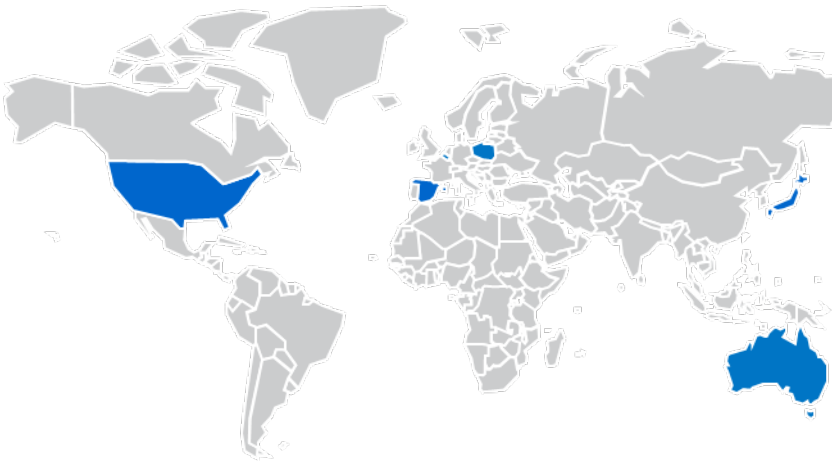
Part 2 of the study is taking place at 17 study centres, across six countries around the world.

For more information on Part 1 and Part 2 of the study, see section 3 “What is happening during this study?”

The following map shows the countries where the study is taking place.

**Part 1**
- Japan – 2 people
- Spain – 5 people

**Part 2**
- Australia – 5 people
- Belgium – 4 people
- Japan – 6 people
- Poland – 6 people
- Spain – 9 people
- US – 11 people



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

In this study, 48 people with haemophilia A – 7 in Part 1 and 41 in Part 2 – are taking part. They are all males, aged 12 years or older.

People could take part in this study if they:
- have severe haemophilia A with or without inhibitors against factor eight
- had been taking replacement factor eight or a bypassing agent to treat their haemophilia A, for at least 24 weeks before the start of the study.

People could not take part in the study if they:
- had treatment for blood clots in the previous 12 months
- had diseases or conditions other than haemophilia A that might have increased their risk of bleeding
- had planned to have a surgery during this study.

## 3. What is happening during this study?

This study has two parts. These two parts have different aims and are using slightly different dosing patterns of emicizumab.

## Part 1

Part 1 of the study began in a small number of people (7) before Part 2 started.

Part 1 of the study was done to see how emicizumab was processed in the body when given once every 4 weeks. Study doctors wanted to see if the level of emicizumab in the blood was high enough to help prevent bleeds when given once every 4 weeks, instead of once every week or once every 2 weeks. They also wanted to see if the level of emicizumab changed over time. Part 1 of the study also looked at the side effects of emicizumab treatment when given once every 4 weeks.

In Part 1 of the study, people were given 6.0 mg/kg of emicizumab (meaning six milligrams of emicizumab for every one kilogram of body weight) once every 4 weeks for a total of at least 24 weeks.

When people were given emicizumab once every week or once every 2 weeks in other Phase 3 studies, they 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. These are called the '**loading doses**'. These loading doses were not given in Part 1 of this study, because the study doctors wanted to look at how emicizumab is processed in the body when given 6.0 mg/kg once every 4 weeks.

When all the people in Part 1 had been treated for at least 6 weeks, the results showed that 6.0 mg/kg of emicizumab given once every 4 weeks may be high enough to help prevent bleeding. The results also showed that there were no additional side effects when emicizumab was given 6.0 mg/kg once every 4 weeks, compared with 1.5 mg/kg once every week or 3.0 mg/kg once every 2 weeks. This meant that Part 2 of the study could start.

## Part 2

Part 2 of the study is being carried out in a larger number of people (41) after all the people in Part 1 had been treated for at least 6 weeks.

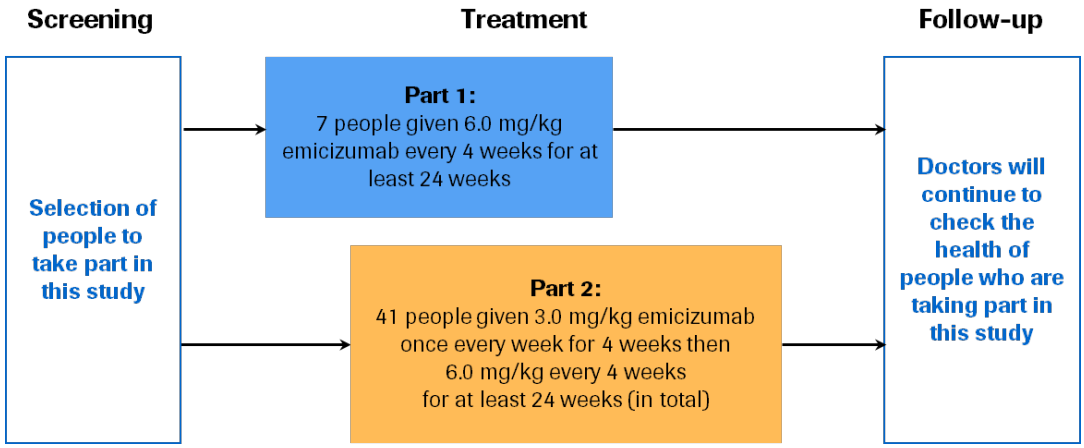
Part 2 of the study aims to find out more about how good emicizumab is at preventing bleeding – and what the side effects are – when given once every 4 weeks.

In Part 2, people were first given the loading doses of 3.0 mg/kg of emicizumab once every week for 4 weeks.

After 4 weeks, people were given 6.0 mg/kg of emicizumab once every 4 weeks for at least 24 weeks. These are called the '**maintenance doses**'.

The results of Part 2 are shown in sections 4 and 5 of this summary.

The following image shows the study design:




This study is still ongoing at the time of writing this summary, so some 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.

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

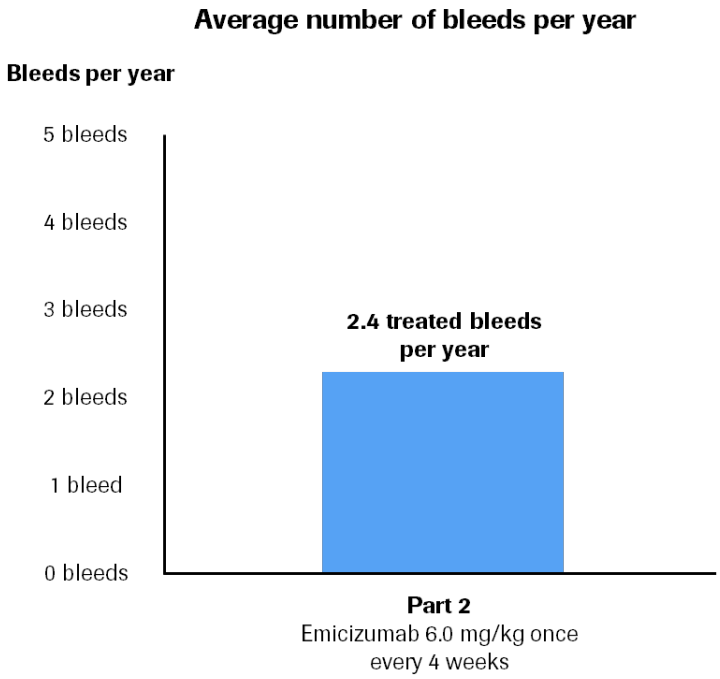
### **Question 1:** How many bleeds do people have when emicizumab is given once every 4 weeks?

If a person has a bleed while taking part in the study, they can treat the bleed with either replacement factor eight (for those without inhibitors against factor eight) or bypassing agents (for those with inhibitors against factor eight). Bleeds that are treated in this way are called '**treated bleeds**'.

Doctors looked at how many treated bleeds people had, on average, over the course of 24 weeks, 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 a year.

Only people in Part 2 are included in these results. This is because Part 2 of the study was designed to find out how many bleeds people had when they were given emicizumab once every 4 weeks.

People in Part 2 who were given emicizumab had, on average, less than three treated bleeds per year (2.4 bleeds). Most people (37 out of 41, 90%) had less than three treated bleeds while taking emicizumab, and more than half of the people (23 out of 41, 56%) had no treated bleeds.




This section only shows the main results from the study up to December 2017. You can find information about all other results on the websites at the end of this summary (see section 8 "Where can I find more information?").

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

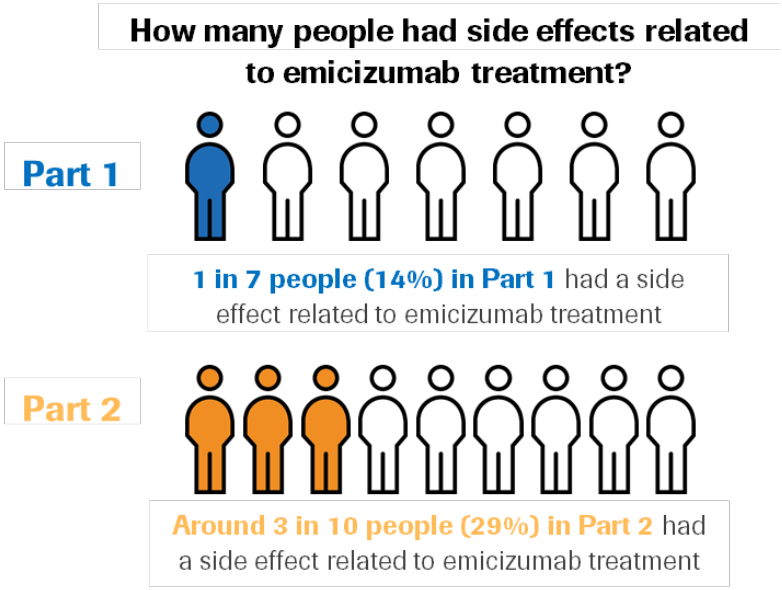
### **Question 2.** How many people had side effects related to emicizumab?

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.
- 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.
- Side effects that were not related to emicizumab treatment are not listed in this summary.

During Part 1 of this study, 1 out of 7 people (14%) had a side effect related to emicizumab treatment that was not considered serious.

During Part 2 of this study, 12 out of 41 people (29%) had a side effect related to emicizumab treatment that was not considered serious.




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 were redness of the skin where the injection was given. This is called an **'injection site reaction'**. Across both parts of the study (Part 1 and Part 2), 11 people had injection site reactions. Nine out of 11 people (82%) had mild reactions. Two out of 11 people (18%) had moderate reactions.

## 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.

During this study, no-one had a **serious side effect** related to the use of emicizumab.

## Common side effects

A side effect is considered 'common' if it is seen in more than 5% of people (1 out of 20) in all treatment groups.

Redness of the skin where the injection was given was the only **common side effect** related to emicizumab seen during this study.

## Other side effects

The following table lists all the side effects in this study that the doctors believed to be related to emicizumab. It also shows the number of people in each part of the study who had each of these side effects.

| Side effect | Part 1 (7 people) | Part 2 (41 people) |
|---|---|---|
| **Injection site reaction** | 1 | 9 |
| **Chills** | 0 | 1 |
| **Redness of the skin** | 0 | 1 |
| **Rash** | 0 | 1 |
| **Feeling dizzy or faint** | 0 | 1 |

You can find information about other side effects that were unrelated to emicizumab (not shown in the section above) on the websites listed at the end of this summary (see section 8 "Where can I find more information?").

## 6. How does this study help research?

The results presented here are from a single study, in two parts, of 48 people aged 12 years and older with haemophilia A. The results are helping doctors to learn more about the effect of less frequent treatment with emicizumab in people with haemophilia A.

Previous studies have shown that emicizumab helps to prevent bleeding in people of all ages with haemophilia A with and without inhibitors against factor eight when given once every week or once every 2 weeks.

The results from this study show that emicizumab given once every 4 weeks helps to prevent bleeding in people with haemophilia A with or without inhibitors against factor eight. The number of treated bleeds people had when given emicizumab once every 4 weeks in the main analysis of this study is similar to the number of treated bleeds people had when given emicizumab once every week or once every 2 weeks in previous studies.

The results also show that around one in three people receiving emicizumab once every 4 weeks in Part 2 of the study had a side effect related to emicizumab treatment. These side effects were mostly injection site reactions. These side effects are similar to those seen in people given emicizumab once every week or once every 2 weeks in previous studies.

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.

At the time of writing this summary, this study is still happening and the doctors are still collecting information.

## 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/NCT03020160
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001094-33/results

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: "Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study". The authors of the scientific paper are: Steven W Pipe, Midori Shima, Michaela Lehle, Amy Shapiro, Sammy Chebon, and others. The paper is published in the journal 'Lancet Haematology', volume number 6, on pages e295–305.

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

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?

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

## Full title of the study and other identifying information

The full title of this study is: “A multicenter, open-label, phase III study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab given every 4 weeks (Q4W) in patients with haemophilia A”.

The study is known as ‘HAVEN 4’.

- The protocol number for this study is: BO39182.
- The ClinicalTrials.gov identifier for this study is: NCT03020160.
- The EudraCT number for this study is: 2016-001094-33.

# 9. Infographic summary

## A study looking at whether emicizumab can prevent bleeding in people aged 12 years and older with haemophilia A when given once every 4 weeks – and whether there are any side effects of taking emicizumab

Roche

This is a summary of the results of a study, written for the general public and the people taking part. This study started in January 2017 and is expected to end in June 2022. Here, we report the results from the main analysis of this study up until December 2017.

### Why is this study being 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.

A medicine called **emicizumab** is the focus of this study. It has been shown in previous studies that emicizumab given once every week or once every 2 weeks can help prevent bleeding in people with haemophilia A.

This study is being done to see whether emicizumab given **once every 4 weeks** can help prevent bleeding in people with haemophilia A. This study is also looking at whether there are any side effects of emicizumab.

### Who is taking part in this study?

This study took place at:

**17** centres across the world

**6** countries around the world


people with haemophilia A are taking part.

They are aged **12** years and older and are all male.

### What is happening in this study?

This study is happening in two parts. The two parts of the study have different aims and are using slightly different dosing patterns of emicizumab.

**Part 1**
7 people

**Emicizumab 6 mg/kg once every 4 weeks** for at least 24 weeks

**Part 1** of the study showed that the amount of emicizumab in the blood may be high enough to prevent bleeding when emicizumab is given once every 4 weeks. It also showed that there were no safety concerns associated with emicizumab when given once every 4 weeks.

This meant that **Part 2** of the study could start.

**Part 2**
41 people

Emicizumab 3 mg/kg once every week for 4 weeks

then

**Emicizumab 6 mg/kg once every 4 weeks** for at least 24 weeks

- If a person had a bleed while taking part in the study, they could treat the bleed with either replacement factor eight (for those without inhibitors against factor eight) or bypassing agents (for those with inhibitors against factor eight).
- To see if emicizumab prevents bleeding, doctors looked at the number of treated bleeds people had in Part 2 of the study.

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

People in Part 2 who were given emicizumab once every 4 weeks had, on average, **2.4** treated bleeds per year.

**2.4** bleeds per year

Most people (**37 out of 41, 90%**) had less than three treated bleeds while taking emicizumab.

**90%**

More than half of people (**23 out of 41, 56%**) had no treated bleeds while taking emicizumab.

**56%**

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

The study doctors believed the side effects reported here may have been related to emicizumab. Side effects that were not reported as related to emicizumab treatment are not listed here.

In **Part 1**, **1 person out of 7** (14%) had a side effect related to emicizumab

In **Part 2**, around **1 in 3 people** (29%) 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). Redness of the skin where the injection was given was the only 'common' side effect related to emicizumab seen during this study. It was not considered serious.

### What did this study tell us?

Emicizumab given once every 4 weeks helps to prevent bleeding in people with haemophilia A. In this study, about one in three people had side effects related to emicizumab, which were mostly redness of the skin where the injection was given.

This study is known as 'HAVEN 4' (NCT03020160) and was organised and paid for by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd.
M-XX-00012637 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 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 which is expected to be effective and cause minimal side effects. |
| Mild side effect | A side effect that causes mild discomfort, lasts for less than 2 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. 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. This 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. |
| Treatment burden | The actions that people with a chronic (long-term) illness must take to treat their condition day-to-day, including the impact these actions have on their functioning, wellbeing, relationships and quality of life. |