Clinical Trial Results – Layperson Summary

A study looking at whether emicizumab can prevent bleeding in people with haemophilia A without inhibitors against factor eight who are aged 12 years and older – and looking at 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 September 2016 and is expected to end in May 2022. This summary includes the results that were collected and analysed in September 2017. At the time of writing this summary, the study is still ongoing – 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** blood disorder that mostly affects men – 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'). This is caused by an abnormal **gene**. 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, especially in their joints and muscles. These bleeds can be caused by minor injuries or may have no obvious cause.

Standard treatment for people with haemophilia A is to replace the inactive factor eight protein with 'replacement factor eight'. Treatment with replacement factor eight 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 **IV injection**).

Replacement factor eight can be given after a bleed has happened to help the bleeding stop. This is called '**on-demand**' treatment.

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

Replacement factor eight remains in the blood for a short, variable period of time depending on how it is processed by each person's body. This means that replacement factor eight only improves clotting for a short period of time. Because of this, when replacement factor eight is given to prevent bleeding it must be given twice a week or more often.

There are many different types of replacement factor eight treatment, and different people may receive different doses.

Some people with haemophilia A get **inhibitors against factor eight**, which stop replacement factor eight treatment from working. In this summary we are only discussing people with haemophilia A who **do not have inhibitors against factor eight**.

This study is being done to see whether a new medicine – emicizumab – can prevent bleeding and help to reduce **treatment burden**, such as frequent injections into a vein. This study is also looking at whether there are any side effects of taking emicizumab.

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 (other than factor eight) found in the blood to restore the function of the missing active 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.

In this study, preventative (prophylactic) emicizumab treatment is being compared with:
- no preventative treatment, and
- preventative (prophylactic) factor eight treatment.

What do doctors want to find out?

Doctors are doing this study to see if emicizumab can reduce the risk of bleeding in people with haemophilia A, compared with no preventative treatment (see section 4 "What are the results of this study?").

Doctors are also doing this study to see if emicizumab can reduce the risk of bleeding in people with haemophilia A compared with previous preventative (prophylactic) factor eight treatment in the same person. To do this, doctors did a **previous study** that looked at people with haemophilia A taking preventative (prophylactic) factor eight treatment and recorded the number of bleeds they had. In this study, these same people then switched to preventative (prophylactic) emicizumab treatment – instead of preventative factor eight treatment. The number of bleeds people have when they are taking emicizumab is compared with the number of bleeds they had when they were taking preventative (prophylactic) factor eight treatment.

Doctors also want to find out how safe emicizumab is when given once every week or once every two weeks – by checking how many people have side effects when taking emicizumab during this study and what these side effects are (see section 5 "What are the side effects?").

What kind of study is this?

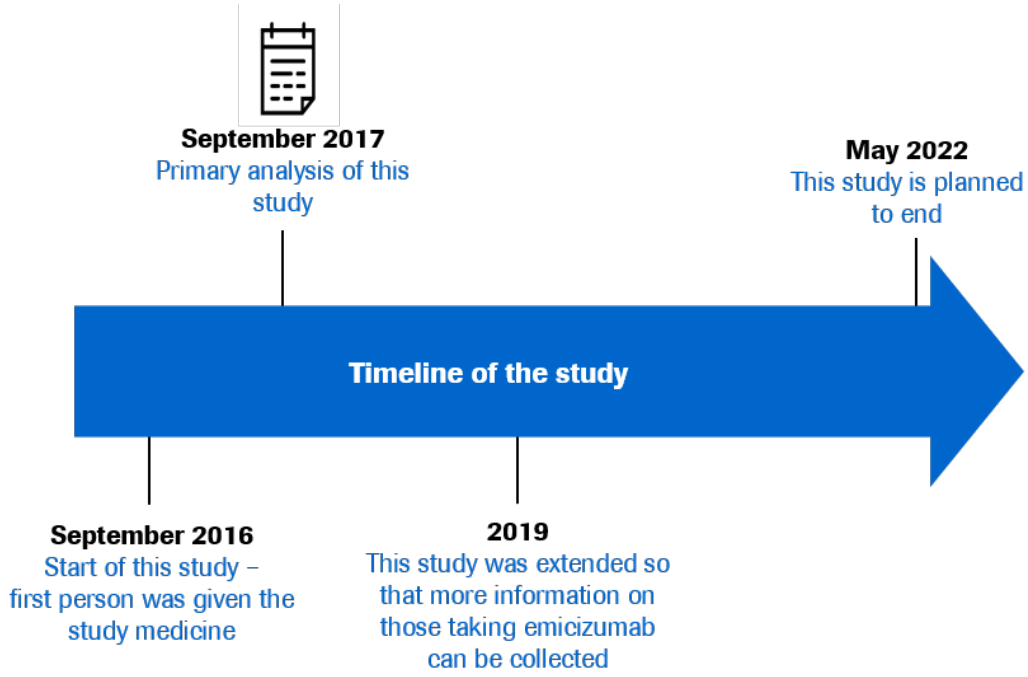
Emicizumab has previously been tested in smaller **Phase 1** and **Phase 2** studies. This is a larger '**Phase 3**' study that aims to show whether emicizumab can prevent bleeding and if there are any side effects of taking emicizumab. If a new drug is shown to be **effective** and have a **favourable safety profile** in a Phase 3 study, the results can be used to gain approval from regulators to make the drug available to people with haemophilia A.

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

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 – whether they are being given emicizumab or no preventative treatment.

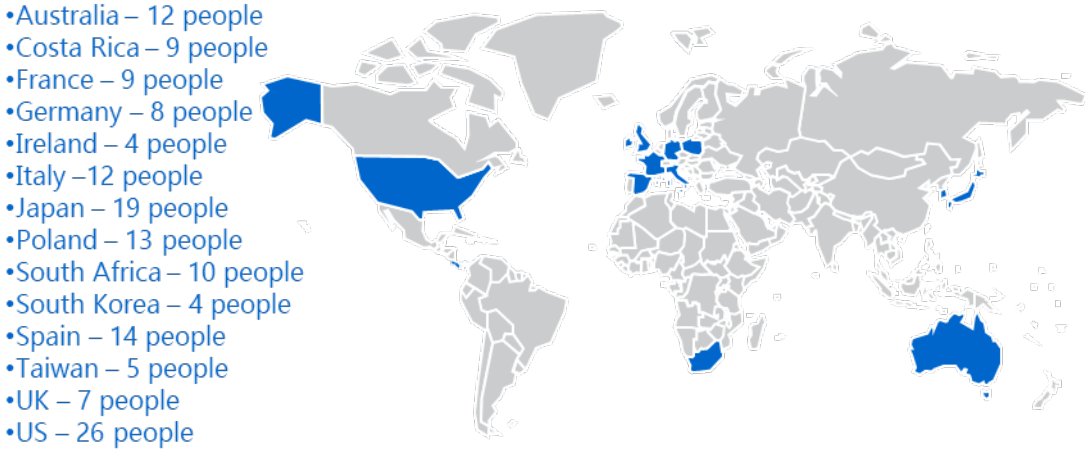
When and where is this study taking place?

The study started in September 2016 and is expected to end in May 2022. This summary includes the results from the primary analysis that were collected and analysed in September 2017 – 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 picture (📅) shows when the results shown in this summary were collected – September 2017.

The study is taking place at 39 study centres, across 14 countries around the world. The following map shows the countries where this study is taking place.



2. Who is taking part in this study?

In this study, 152 people with haemophilia A are taking part. They are all aged 12 years or older, and are all male.

People could take part in the study if they:

- have severe haemophilia A **without inhibitors against factor eight**
- weighed at least 40 kilograms at 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.

3. What is happening during this study?

People who were taking no preventative factor eight treatment before the start of this study have been assigned by chance (**randomised**) into one of three treatment groups – Group A, Group B, or Group C. People who were taking preventative factor eight before the start of this study have been assigned to Group D.

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 four weeks. These are called the '**loading doses**'. After four weeks, they started taking 1.5 mg/kg emicizumab once every week for at least 24 weeks. These are called the '**maintenance doses**'.

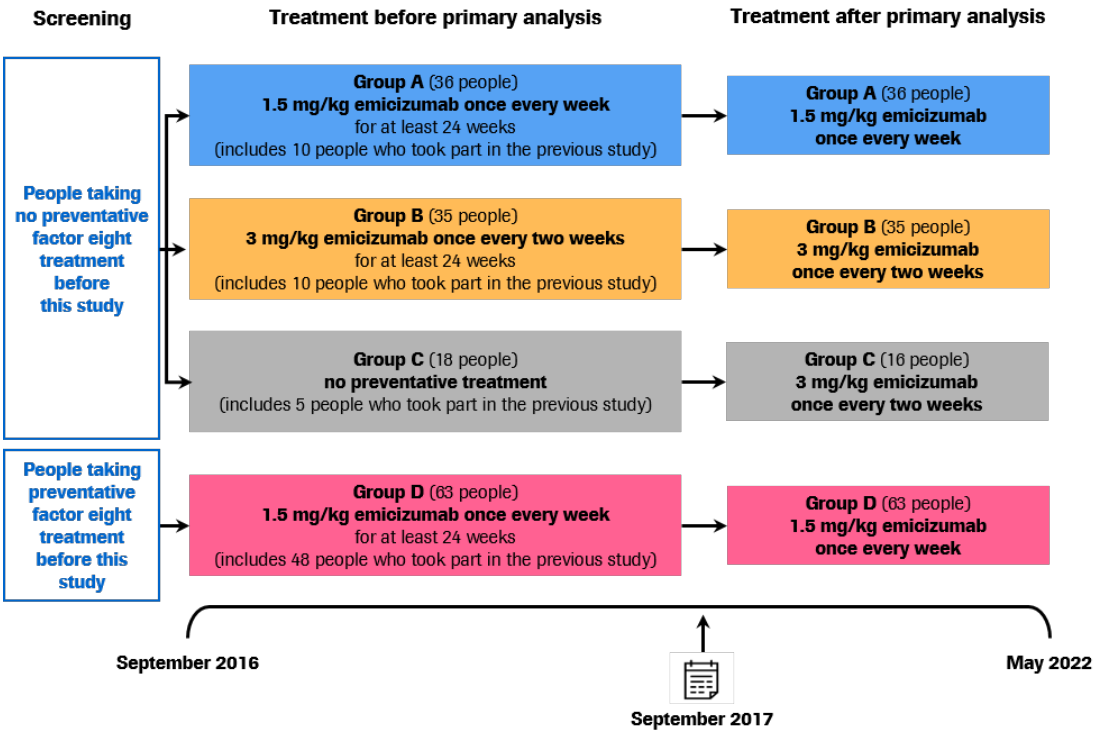
- **Group B** – as in Group A, these people were first given loading doses of 3 mg/kg emicizumab once every week for four weeks. After four weeks, they started taking maintenance doses of 3 mg/kg emicizumab once every two weeks for at least 24 weeks.

- **Group C** – these people did not receive any preventative treatment for the first 24 weeks of the study. After 24 weeks, people in Group C could start taking emicizumab. If they switched to emicizumab, they started with loading doses of 3 mg/kg emicizumab once every week for four weeks. After four weeks, they started taking maintenance doses of 3 mg/kg emicizumab once every two weeks for at least 24 weeks, as in Group B.

- **Group D** – these people were taking preventative factor eight before the start of this study. People in Group D were first given loading doses of 3 mg/kg emicizumab once every week for four weeks. After four weeks, they were given a maintenance dose of 1.5 mg/kg emicizumab once every week for at least 24 weeks.

Everyone in the study could receive 'on-demand' replacement factor eight treatment if they had a bleed.

The following image shows the study design:



The calendar symbol on the picture (📋) shows when the results shown in this summary were collected – September 2017.

People in Group C did not receive any preventative treatment for the first 24 weeks of the study but, after 24 weeks, they could choose to begin treatment with emicizumab. At the time of these results, 16 of the 18 people in Group C had started taking emicizumab. Of the two people not taking emicizumab, one person was unreachable and one person was waiting to begin taking emicizumab.

This study is still ongoing. When the study finishes, people taking part in this study may either continue to take emicizumab, or change to a different treatment if they prefer.

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

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

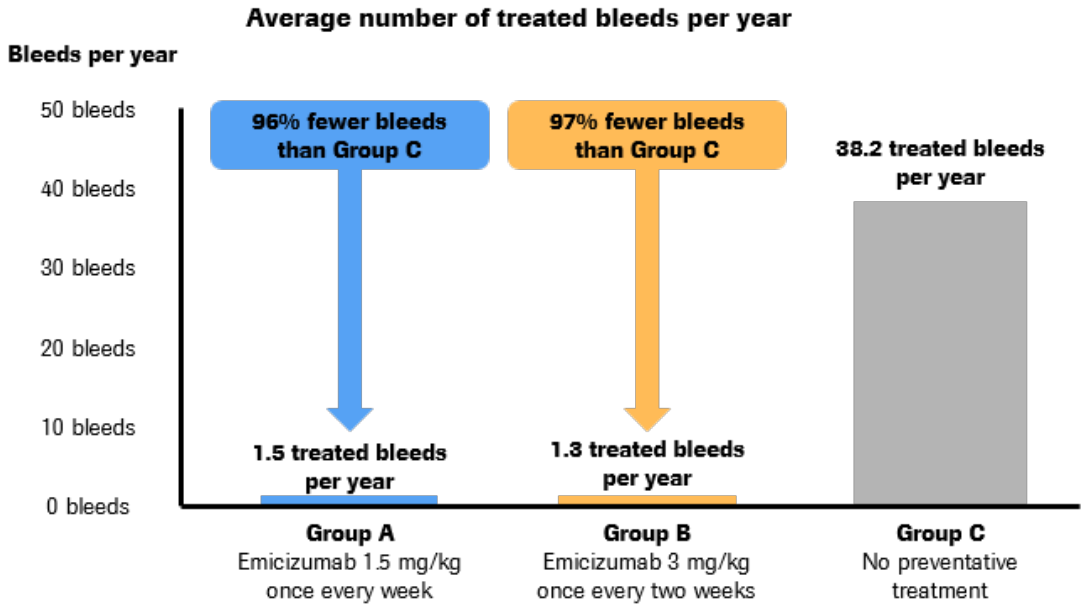
If a person has a bleed while taking part in the study, they can treat the bleed with on-demand factor eight. Bleeds that are treated in this way are called '**treated bleeds**'.

Doctors have looked at how many **treated bleeds** people in Group A and Group B 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 primary analysis, some people in the study had not been treated for a full year. If this was the case, doctors used the numbers of treated bleeds people had during the time they received treatment and estimated how many treated bleeds that person could potentially have over the course of a year.

People in Group C, who were not receiving preventative treatment, had on average 38.2 treated bleeds a year. All of the people in Group C had at least one treated bleed.

People in Group A, who were given emicizumab once every week, had on average 1.5 treated bleeds a year. More than half of them (20 out of 36 people, 56%) had no treated bleeds.

People in Group B, who were given emicizumab once every two weeks, had on average 1.3 treated bleeds a year. Nearly two thirds of them (21 out of 35 people, 60%) had no treated bleeds.

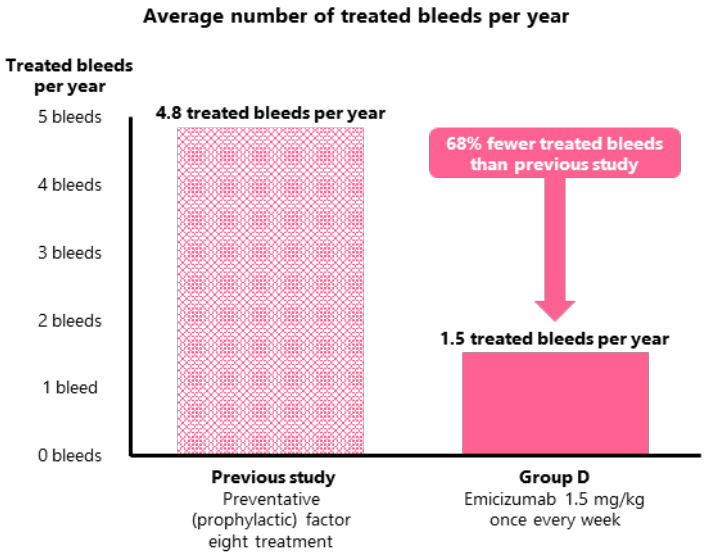


Question 2: How many bleeds did people have in this study compared with the number of bleeds they had when they were taking preventative (prophylactic) factor eight treatment in the previous study?

Doctors have also looked at how many treated bleeds people had when they were taking emicizumab in this study compared with how many treated bleeds the same people had when they were taking preventative (prophylactic) factor eight treatment in the previous study. This was done by looking at the 48 people from Group D, who were taking preventative (prophylactic) factor eight treatment in the previous study. Results from these 48 people are included here.

These 48 people had, on average, 1.5 treated bleeds per year when they were taking emicizumab in this study compared with 4.8 treated bleeds per year when they were taking preventative (prophylactic) factor eight treatment in the previous study.

This means that they had 68% fewer treated bleeds when they were taking emicizumab than they did when they were taking preventative (prophylactic) factor eight treatment.



In the previous study, 40% of people (19 out of 48) receiving preventative (prophylactic) factor eight treatment had no treated bleeds. After switching to emicizumab, 54% of people (26 out of 48) had no treated bleeds.

This section only shows the key results from the study up to September 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 were the side effects reported in the primary analysis of this study?

Question 3: How many people have had side effects?

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 are related to emicizumab treatment.
- Not all of the people in this study have side effects. People who do have side effects do not have all of those listed below.
- 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 are from this single study. Therefore, the side effects shown here may be different from those seen in other studies, or those that appear on the medicine leaflet. The following sections list side effects that the doctors in this study thought were related to emicizumab treatment. Side effects that were not related to emicizumab treatment are not listed in this document.

In Group C, only people who have switched to emicizumab after at least 24 weeks on the study are included in this section. People in Group C did not receive any preventative

treatment for the first 24 weeks of the study but, after 24 weeks, they could choose to begin treatment with emicizumab.

Serious side effects

A side effect is considered 'serious' if it is life-threatening, needs hospital care, causes lasting problems, or causes death.

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

Most common side effects

During this study, around one in three people (33%) had a side effect related to emicizumab treatment that was not considered serious. The only side effect related to emicizumab that was considered 'common', meaning it was seen in more than 5% of people (1 out of 20) in all treatment groups, was redness of the skin where the injection was given – also called 'injection site reaction'.

There were other side effects that happened during this study, such as coughs or colds, but the study doctors did not believe they were related to emicizumab treatment.

One person in Group B (1 of 35 people, 3%) decided to stop taking emicizumab because of several mild side effects, which were not considered to be serious. The doctor treating this person believes that these side effects were related to emicizumab treatment.

Other side effects

No-one in the study developed new inhibitors against factor eight.

You can find information about other, less common, side effects (not shown in the sections 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 information presented here is from a single study of 152 people with haemophilia A without inhibitors against factor eight who are aged 12 years and older. The results are helping doctors to learn more about the effect of emicizumab in people with haemophilia A without inhibitors against factor eight.

Previous studies have shown that emicizumab can prevent bleeding in people of all ages with haemophilia A with inhibitors against factor eight when given once every week.

The results from this study show that emicizumab, given once every week or once every two weeks, better prevented bleeding than no preventative (on-demand) treatment and preventative (prophylactic) factor eight treatment in people with haemophilia A without inhibitors against factor eight. The results also show that emicizumab did not cause any serious side effects.

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.

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 website listed below:

- https://clinicaltrials.gov/ct2/show/NCT02847637

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: 'Emicizumab Prophylaxis in Patients Who Have Hemophilia A Without Inhibitors'. The authors of the scientific paper are: J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Négrier, M. Niggli and others. The paper is published in 'The New England Journal of Medicine', volume number 379, on pages 811–822.

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 Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)'.

The study is known as 'HAVEN 3'.

- The protocol number for this study is: BH30071.
- The ClinicalTrials.gov identifier for this study is: NCT02847637.
- The EudraCT number for this study is: 2016-004366-25.

9. Infographic summary

A study looking at whether emicizumab can prevent bleeding in people with haemophilia A without inhibitors against factor eight who are aged 12 years and older – and looking at 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 who took part in the study.
Here we report the results from the primary analysis of this study up until September 2017 – the study is ongoing to collect long-term data.

Why is this study being done?

Haemophilia A is a rare inherited bleeding disorder. People with haemophilia A have little to no activity of a protein called 'clotting factor eight'. Without this active protein, the blood cannot clot properly meaning that people with haemophilia A have many bleeds.

A medicine called **emicizumab** is the focus of this study. Doctors are doing this study to see if emicizumab given regularly can prevent bleeding in people with haemophilia A, and to look at whether there are any side effects of taking emicizumab. Side effects are unwanted medical problems that can happen while taking a treatment.

Who is taking part in this study?

This study is taking place at:

39 centres across

14 countries around the world

152 people with haemophilia A are taking part.

They are all aged 12 years or older, and are all male.

What is happening in this study?

People who were taking no preventative treatment before the start of this study have been randomised into one of three treatment groups; A, B or C. People who were taking a preventative treatment called 'replacement factor eight' before the start of this study were assigned to Group D.

Group A
36 people

Emicizumab 3 mg/kg once every week for four weeks

then

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

Group B
35 people

Emicizumab 3 mg/kg once every week for four weeks

then

Emicizumab 3 mg/kg once every two weeks for at least 24 weeks

Group C
18 people

No preventative treatment for at least 24 weeks

Group D
63 people

Emicizumab 3 mg/kg once every week for four weeks

then

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

- To see if emicizumab prevents bleeding, doctors compared the number of bleeds in Groups A and B with the number of bleeds in Group C.
- After 24 weeks, 16 people in Group C started taking emicizumab (same dosing as Group B).
- Doctors also wanted to see if emicizumab was better at preventing bleeding than replacement factor eight by comparing the number of bleeds people had in Group D with how many bleeds the same people had when they were previously receiving preventative factor eight treatment.

What were the results from the primary analysis of this study?

People taking emicizumab had **96% fewer treated bleeds** than people taking no preventative treatment.

Group A (emicizumab once weekly)	Group B (emicizumab every two weeks)	Group C (no preventative treatment)
1.5 bleeds per year	1.3 bleeds per year	38.2 bleeds per year

In **Group D**, people had **68% fewer treated bleeds** when taking emicizumab than they did when they were taking preventative factor eight.

This study (emicizumab once weekly)	Previous study (preventative factor eight)
1.5 bleeds per year	4.8 bleeds per year

What side effects were reported in the primary analysis of this study?

The side effects listed here are those the study doctors believed may have been related to the study treatment - emicizumab. There were other side effects, such as coughs or colds, but the study doctors did not believe they were related to emicizumab treatment.

One in three people (33%) had a side effect related to emicizumab treatment

The only treatment-related side effect considered 'common', meaning it was seen in more than 5% of people (1 out of 20), was redness of the skin where the injection was given – also called 'injection site reaction'.

The other side effects related to the study treatment seen in more than one person were headache (four people) and nausea (two people).

How does this study help research?

These results show that emicizumab given once every week or once every two weeks better prevented bleeding compared with no preventative treatment or preventative factor eight treatment in people with haemophilia A – and did not cause any serious side effects.

This study is known as 'HAVEN 3' (NCT02847637) and was organised and paid for by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd.
M-XX-00012633 Date of preparation: March 2023.

10. Glossary

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.
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.
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.
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.
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, 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.
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.