Clinical Trial Results – Layperson Summary

A study to look at the side effects of taking emicizumab▼ in people with haemophilia A with inhibitors against factor eight – and how well emicizumab prevented bleeding

See the end of the summary for the full title of the study, and a 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 2017 and finished in November 2020. This summary was written after the study had ended.

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

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

Contents of this summary

Thank you to the people who took part in this study

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

▼ Emicizumab is subject to additional monitoring. This will allow quick identification of new safety information. If you, or someone you are caring for, has a side effect while taking this treatment, you should tell your/their doctor immediately.

1. General information about this study

What is haemophilia A?

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.

How is haemophilia A treated?

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

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

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

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

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

What are inhibitors against factor eight?

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.

Everyone in this study had inhibitors against factor eight.

What is the study medicine?

The study medicine is called 'emicizumab' (HEMLIBRA®). It is an alternative treatment for haemophilia A.

- You say this as 'em – me – sih – zuh – mab'.
- Emicizumab acts as a substitution therapy.
- Emicizumab works by acting on clotting proteins found in the blood to substitute for factor eight.
- Emicizumab improves the ability of the blood to make clots, which means that bleeding is less likely in people with haemophilia A.
- Emicizumab is a preventative (prophylactic) treatment. This means that it is given on a regular basis to prevent bleeding.
- Emicizumab is given as an injection under the skin. This is different than replacement factor eight treatment or bypassing agents, which are given as an injection into a vein.
- It has been shown in previous studies that emicizumab given once every week, once every 2 weeks, or once every 4 weeks, helps to prevent bleeding in people with haemophilia A.
- Emicizumab is effective in people with inhibitors against factor eight and people without inhibitors against factor eight and has been approved by the health authorities for treatment of these people.

If you would like to read more about previous studies with emicizumab, please see section 8 "Where can I find more information?".

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

What did doctors want to find out?

Doctors did this study to look at side effects in people with inhibitors against factor eight who were taking emicizumab once every week, for 2 years (see section 4 "What side effects were reported in this study?"). These people were aged 12 years or older. This was the main objective of this study because it is important to continue to check the side effects of a medicine even after it is approved for doctors to give to patients.

Although it was not the main objective, this study also looked at how many bleeds people with inhibitors against factor eight had when taking emicizumab once every week, for 2 years (see section 5 "What were the other results of this study?").

What kind of study was this?

This study was a **'Phase 3b'** study. This means that the study was started after the drug company had asked for approval from health authorities for doctors to give the drug to patients, but before this approval was given.

This was an **'open label'** study. This means that both the doctors and the people who took part in the study knew which medicine they were receiving. In this study, everyone who took part received emicizumab once every week.

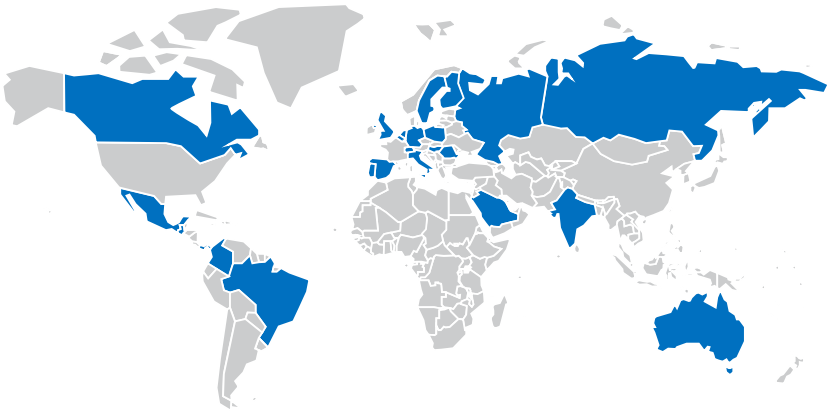
When and where did this study take place?

This study started in September 2017 and ended in November 2020. This summary was written after the study had ended.

This study took place at 72 study centres across 24 countries.

The following map shows the countries where the study took place.

- Australia – 7 people
- Belgium – 4 people
- Brazil – 10 people
- Canada – 10 people
- Colombia – 5 people
- Finland – 2 people
- Germany – 13 people
- Guatemala – 2 people
- Hungary – 3 people
- India – 30 people
- Israel – 4 people
- Italy – 27 people
- Mexico – 18 people
- Netherlands – 5 people
- Panama – 4 people
- Poland – 3 people
- Portugal – 4 people
- Romania – 1 person
- Russian Federation – 11 people
- Saudi Arabia – 7 people
- Spain – 12 people
- Sweden – 4 people
- Switzerland – 1 person
- United Kingdom – 8 people



2. Who took part in this study?

In this study, 195 people with haemophilia A took part. They were all males, aged 12 years or older.

People could take part in this study if they:

- had haemophilia A with 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:

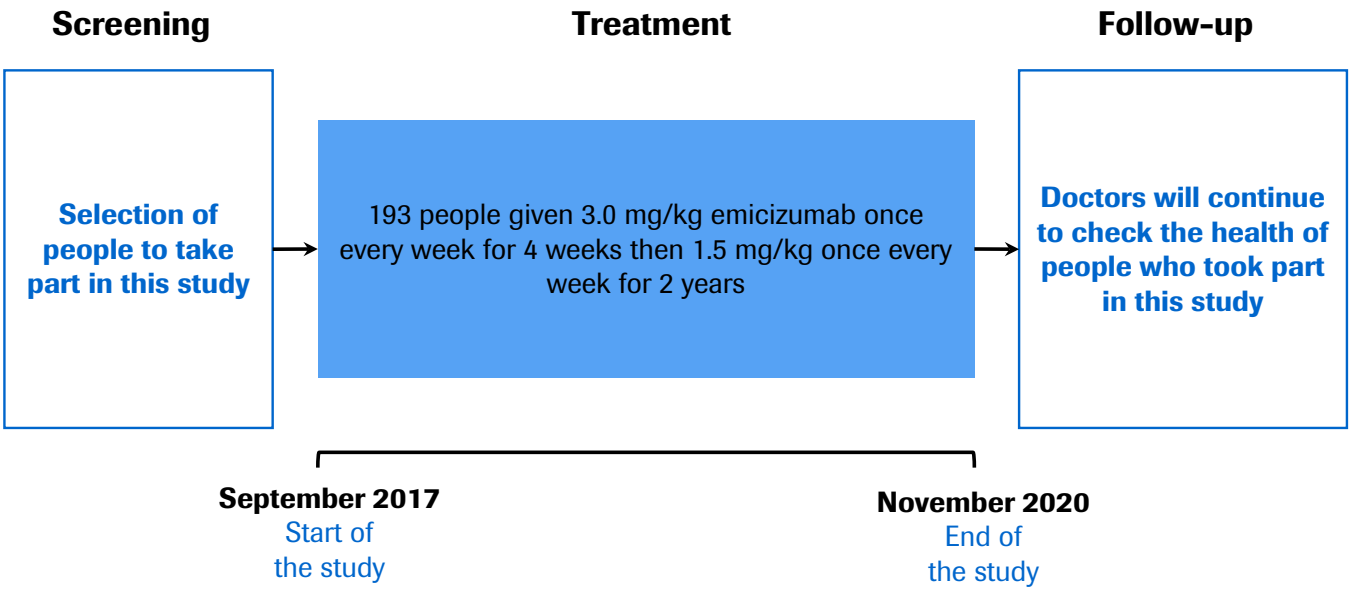
- had treatment for blood clots in the previous 12 months
- had diseases or conditions other than haemophilia A that might have increased their risk of bleeding
- were having or planning to have therapy to get rid of their inhibitors against factor eight (also known as **'immune tolerance induction therapy'**) during the study.

3. What happened during this study?

While this study planned to have 195 people participate, two people dropped out before they received emicizumab. The other 193 people in this study were first given 3.0 mg/kg of emicizumab once every week for 4 weeks, to quickly build up the levels of emicizumab in the body. These are called the '**loading doses**'.

After the first 4 weeks, people were given 1.5 mg/kg of emicizumab once every week for 2 years. These are called the '**maintenance doses**'.

People in the study took emicizumab for at least 2 years. When the study finished, the people who took part were asked to go back to their study centre for more visits – to continue to check their overall health. People who took part could continue to take emicizumab or change to a different treatment if they preferred. Look below to see more information about what happened in the study.



4. What side effects were reported in this study?

Unwanted medical problems can sometimes occur during a study. These are known as '**adverse events**' and may or may not be related to the study treatment. If doctors believe an adverse event is related to the study treatment, it is also known as a '**side effect**' of the treatment.

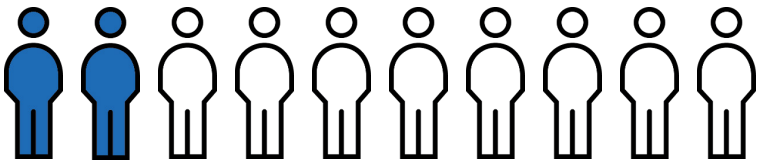
Question 1: What side effects did people have while receiving emicizumab?

Adverse events that are related to the study treatment are also known as side effects.

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

A total of 35 out of 193 people (18%) in this study had side effects of emicizumab.

How many people had side effects related to emicizumab treatment?



Around 2 in 10 people (18%) had a side effect related to emicizumab treatment

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 of emicizumab were redness of the skin where the injection was given. This is called an **'injection site reaction'**. During the study, 19 people had injection site reactions that were side effects of emicizumab treatment. Seventeen out of 19 people (89%) had mild reactions. Two out of 19 people (11%) had moderate reactions.

The table below lists all the side effects of emicizumab in this study. It also shows the number of people in the study who had each of these side effects.

Side effects of emicizumab	Number of people who had this side effect (out of 193)
Injection site reaction	19
Itchiness	2
Sleepiness	2
Tiredness	1
Skin irritation	1
Red, itchy welts	1
Change in sense of taste	1
Hoarseness	1
Shortness of breath	1
Throat irritation	1
Bruising	1
Bruising and swelling after a procedure	1
Eye pain	1
Abdominal pain	1
Pus at the site of a tube for giving blood products and fluids	1
Increase in levels of liver proteins	1
Erectile dysfunction	1

Serious side effects of emicizumab

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

One person in this study had a **serious side effect** that the study doctor believed could be related to emicizumab. This serious side effect was pus at the site of a tube for giving blood products and fluids (a **'central venous access device'**) that had been in place for 8 years.

Common side effects of emicizumab

A side effect is considered 'common' if it is seen in more than 5% of people (1 out of 20). Injection site reactions were the only **common side effect** seen during this study.

Question 2: What adverse events did people have while receiving emicizumab, that were not related to emicizumab?

Some people in the study had adverse events, which are unwanted medical problems (such as a cold, or a fall) that may happen during the study.

- In this section, only adverse events that study doctors believed were not related to emicizumab are included. This is because the adverse events that study doctors believed were related to emicizumab (side effects) are reported in question 1.

Like side effects, adverse events can vary from mild to serious and may vary from person to person.

During the study, 159 out of the 193 people who received emicizumab had adverse events that study doctors believed were not related to emicizumab.

Serious adverse events that were not related to emicizumab

During the study, 30 out of 193 people had serious adverse events that study doctors believed were not related to emicizumab.

Two people died during this study. These deaths were not related to emicizumab. One person died due to head injuries, and one person died due to a lung infection, after being diagnosed with cancer.

During the study, one person decided to stop taking emicizumab because of an adverse event. This person had kidney damage. The study doctors believed this damage was not related to emicizumab.

Common adverse events that were not related to emicizumab

This table lists all the **common adverse events** in this study that study doctors believed were not related to emicizumab, and the number of people who had each of these adverse events.

Common adverse events that were not related to emicizumab	Number of people who had this adverse event (out of 193 people)
Joint pain	33
Cold	30
Headache	29
Fever	21
Flu	16
Cough	12
Fall	12
Injury to a limb	10

Question 3: Did anyone have a blood clot while receiving emicizumab?

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

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

Study doctors wanted to check if anyone had similar clotting problems in this study. Two people in this study had blood clots (thrombotic events). The study doctors believed these blood clots were not related to emicizumab. One person had a heart attack, and one person had a very big clot in their mouth after having their tooth taken out. No one in this study had a microscopic blood clot (TMA).

Question 4: Did anyone have an allergic reaction while receiving emicizumab?

Allergic reactions can be a serious side effect of medicines like emicizumab, so the study doctors checked for these during the study. No-one in this study had an allergic reaction.

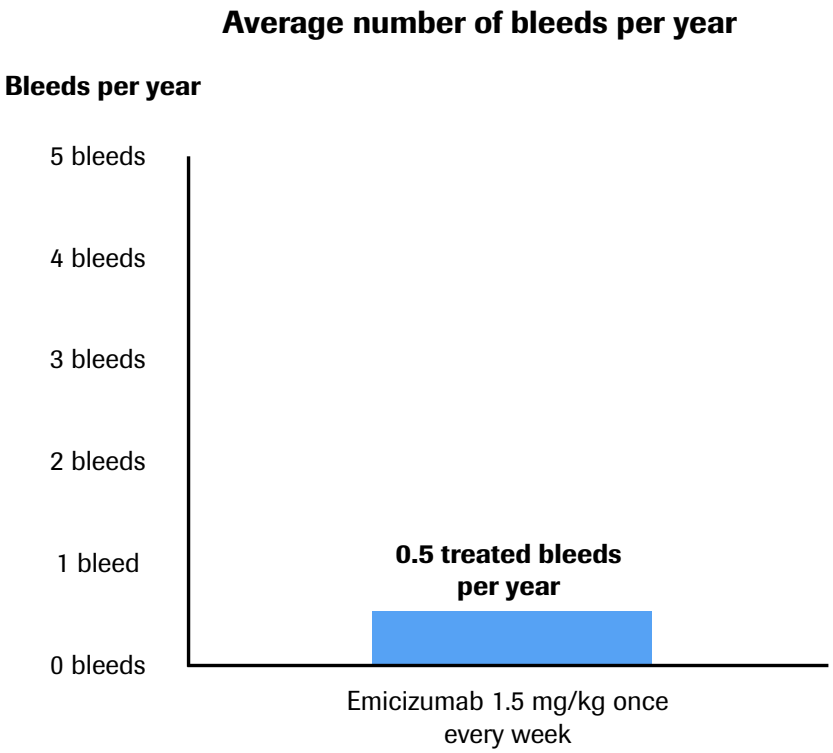
5. What other results were reported in this study?

Question 5: How many bleeds did people with haemophilia A with factor eight inhibitors have when given emicizumab once every week for 2 years?

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

Study doctors looked at how many treated bleeds people had, on average, over the course of 2 years, when taking emicizumab to prevent bleeding. Doctors then used the numbers of treated bleeds people had during this time and estimated how many treated bleeds that person would be likely to have over the course of an average year. These results represent everyone who took part in the study, including the two people who took part in the study but dropped out before receiving emicizumab. This was agreed before the study began.

People had, on average, less than one treated bleed per year (0.5 bleeds). This means that, on average, people had around one treated bleed every 2 years.



Study doctors also looked at how many people in the study did not have any treated bleeds over the 2 years of receiving emicizumab. Over the 2 years of treatment, most people (161 out of 195, 83%) had zero treated bleeds. This table shows how many bleeds people had over the 2 years of receiving emicizumab.

Number of treated bleeds over 2 years of treatment	People who had this number of treated bleeds (out of 195) over 2 years of treatment
0 bleeds	161
1–3 bleeds	24
4–10 bleeds	8
>10 bleeds	2

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

6. How does this study help research?

The results presented here are from a single study of 195 people aged 12 years and older with haemophilia A, with inhibitors against factor eight. The results are helping doctors to learn more about emicizumab given once every week to a large number of people over a long time period (2 years).

The results show that around two in ten people receiving emicizumab once every week over 2 years had a side effect related to emicizumab treatment. These side effects were mostly injection site reactions. One person had a serious side effect that the study doctor

thought might be related to emicizumab (pus at the site of a tube for giving blood products and fluids).

No single study can tell us everything about the risks and benefits of a medicine. It takes many people taking part in several studies to find out what we need to know.

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

7. Are there plans for other studies?

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

8. Where can I find more information?

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

- https://clinicaltrials.gov/ct2/show/NCT03191799
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004366-25/results

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: "STASEY: a long-term Phase IIIb, multicenter, single-arm study of emicizumab prophylaxis in people with hemophilia A with factor VIII inhibitors". The authors of the scientific paper are: Víctor Jiménez-Yuste, Flora Peyvandi, Robert Klamroth, Giancarlo Castaman, Chandrakala Shanmukhaiah, and others. The paper is published in the journal of Research and Practice in Thrombosis and Haemostasis (2022), volume number 6, e-number e12837; the direct web link is https://doi.org/10.1002/rth2.12837.

Where can I find more information about previous studies with emicizumab?

The HAVEN 1–4 studies helped the health authorities decide to approve emicizumab for treating people with haemophilia A. You can read summaries of these studies on the ForPatients platform.

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.

Full title of the study and other identifying information

The full title of this study is "A Study to Evaluate the Safety and Tolerability of Prophylactic Emicizumab in Hemophilia A Patients With Inhibitors (STASEY)".

The study is known as 'STASEY'.

- The protocol number for this study is: MO39129.
- The ClinicalTrials.gov identifier for this study is: NCT03191799.
- The EudraCT number for this study is: 2016-004366-25.

9. Infographic summary

A study to look at the side effects of taking emicizumab▼ in people with haemophilia A with inhibitors against factor eight – and how well emicizumab prevented bleeding

This is a summary of the results of a study, written for the general public and the people taking part. This study started in September 2017 and finished in November 2020. This summary was written after the study had ended.

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 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 is effective in people with inhibitors against factor eight and has been approved by the health authorities for their treatment. It is important to continue to check the safety of a medicine even after it is approved.

Doctors did this study to look at the side effects of emicizumab given once every week in people with haemophilia A with inhibitors against factor eight, and to look at how well emicizumab prevented bleeding.

Who took part in this study?

This study took place at:

72 centres across the world

24 countries around the world

195 people with haemophilia A took part.

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

What happened in this study?

Study treatment
193 people

Emicizumab 3 mg/kg once every week for 4 weeks (loading dose)

then

Emicizumab 1.5 mg/kg once every week for 2 years (maintenance dose)

- While 195 people signed up to this study, two people dropped out before receiving the study medicine.
- Everyone in this study received the same treatment.
- Unwanted medical problems can sometimes occur during a study. These are known as 'adverse events' and may or may not be related to the study medicine.
- If doctors believe an adverse event is related to the study medicine, it is also known as a 'side effect'.
- Doctors looked at how many side effects and adverse events people had while receiving emicizumab.
- If a person had a bleed while taking part in the study, they could treat the bleed with bypassing agents. 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.

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

Side effects related to emicizumab

Around **2 in every 10 people (18%)** 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).** Injection site reaction (redness of the skin where the injection was given) was the only 'common' side effect related to emicizumab – the majority of symptoms were mild.

Serious side effects related to emicizumab

One person had a serious side effect that the study doctor believed could be related to emicizumab – pus at the site of a tube for giving blood products and fluids that had been in place for 8 years.

What adverse events were reported in this study, that were not related to the study medicine?

Common adverse events not related to emicizumab

Common adverse events in this study that were not related to emicizumab were: joint pain, cold, headache, fever, flu, cough, fall, and injury to a limb.

Serious adverse events not related to emicizumab

Around **1 or 2 in every 10 people (16%)** had a serious adverse event not related to emicizumab.

Two people died during this study. These deaths were unrelated to emicizumab. One person died due to head injuries, and one person died due to a lung infection, after being diagnosed with cancer.

During the study, one person decided to stop taking their medicine because of kidney damage. The study doctors believed this damage was not related to emicizumab.

Did anyone have a blood clot while receiving the study medicine?

Two people in this study had blood clots (thrombotic events). The study doctors believed these blood clots were not related to emicizumab. One person had a heart attack, and one person had a very big clot in their mouth after having their tooth taken out.

What other results were reported in this study?

The two people who took part in the study but dropped out before receiving emicizumab are included in these results (as agreed before the study began).

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

0.5 bleeds per year

Most people (161 out of 195) had zero treated bleeds over the 2 years.

33% had zero treated bleeds

What did this study tell us?

The results show that around two in ten people receiving emicizumab once every week over 2 years had a side effect related to emicizumab treatment, mostly injection site reactions. One person had a serious side effect that the study doctor thought might be related to emicizumab (pus at the site of a tube for giving blood products and fluids).

This study is known as 'STASEY' (NCT03191799) and was organised and paid for by F. Hoffmann-La Roche.
M-XX-00008059 ¦ Date of preparation: November 2022.

▼ Emicizumab is subject to additional monitoring. This will allow quick identification of new safety information. If you, or someone you are caring for, has a side effect while taking this treatment, you should tell your/their doctor immediately.

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

10. Glossary

Activated prothrombin complex concentrate	A type of bypassing agent to help the blood clot in people who have inhibitors against factor eight.
Adverse event	An unwanted medical problem that happens when taking a medicine. It may or may not be related to the medicine.
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.
Central venous access device	A device that is inserted into the body through a vein to enable the administration of fluids, blood products, medication and other therapies to the bloodstream.
Clinical trial	When researchers give a group of people a medicine to find out more information about how the medicine works, if it helps to improve people's condition, and if it causes any side effects. The researchers regularly follow up with the people taking the medicine and perform medical tests.
Common side effect or adverse event	A side effect or adverse event that is seen in more than 5% of people (1 out of 20).
Gene	Genes are units of DNA inherited from our parents that contain all the information needed to make people who they are – from the colour of someone's eyes to their blood type. DNA is the code that carries the instructions to build all known living organisms, from bacteria to humans.
Immune tolerance induction therapy	A method for removing inhibitors against factor eight. Replacement factor eight is given in small doses to begin with. The dose is gradually increased. By doing this, the immune system learns to tolerate the factor eight, and stops making inhibitors against factor eight. Immune tolerance induction does not always work.
Inherited	Passed on from one generation to the next through certain genes.
Inhibitors against factor eight	Antibodies produced as a reaction by the body's immune system in response to treatment with replacement factor eight. Inhibitors against factor eight can stop replacement factor eight treatment from working to prevent bleeds. Inhibitors against factor eight often develop at a young age when children are first treated with replacement factor eight.
Injection site reaction	Redness, pain or swelling of the skin at the site where an injection was given.

IV injection	Intravenous injection. An injection into a vein.
Loading dose	An initial higher dose of a medicine that may be given at the beginning of a course of treatment to increase levels of the medicine in the blood quickly before dropping to a lower maintenance dose of that same medicine.
Maintenance dose	The amount of medication given to maintain a level of the medicine in the blood that is expected to be effective and cause minimal side effects.
Mild side effect or adverse event	A side effect or adverse event that causes mild discomfort, lasts for less than 2 days, and does not need any treatment.
Moderate side effect or adverse event	A side effect or adverse event that causes mild to moderate limitation in activity, may cause the person to need some assistance, and needs little or no treatment.
On-demand treatment	Treatment given 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 3b trial	A clinical trial to collect more information on how effective and safe the new medicine is. Phase 3b trials start after the drug company has asked for approval for doctors to give the new medicine to patients, but before this approval has been given.
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.
Serious side effect or adverse event	A side effect or adverse event that is life-threatening, needs hospital care, causes lasting problems and severe limitation of activity, or causes death.

Side effect	An unwanted medical effect that happens when taking a medicine and is believed by doctors to be related to the medicine.
Thrombotic event	An event that occurs when a blood clot forms and blocks a blood vessel.
Thrombotic microangiopathy (TMA)	Formation of a very small – microscopic – blood clot.
Treated bleed	A bleed treated with replacement factor eight or bypassing agents.