Clinical Trial Results – Layperson Summary

A study looking at whether emicizumab▼ can prevent bleeding in people with haemophilia A with inhibitors against factor eight who are aged 12 years and older – and whether there are any side effects of taking emicizumab

See the end of the summary for the full title of this study, and a hyperlinked **glossary** of medical terms.

About this summary

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

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

This study started in November 2015 and finished in December 2020. Whilst the study has already finished, this summary focuses on the published results up until October 2016 when the main analysis took place. The final study results are similar to the results of the main analysis.

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

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

Contents of this summary

Thank you to the people who took part in this study

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

▼ 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** blood disorder caused by an abnormal **gene**. It mostly affects men and boys – less than 1% of people with severe haemophilia A are female. People with haemophilia A have little to no activity of a **protein** in the blood called 'clotting factor eight' (also seen as 'FVIII'). Without this active protein, the blood cannot clot normally. This means that people with haemophilia A can have many bleeds that can last for a long time, including in their joints and muscles. These bleeds can be caused by minor injuries or may have no obvious cause.

How is haemophilia A treated?

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

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

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

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

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

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

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. Preventative (prophylactic) bypassing agents have limitations and do not always protect against bleeds in all people with haemophilia A with inhibitors against factor eight. All people taking part in this study have **inhibitors against factor eight**.

Why was this study done?

This study was done to see whether a new medicine – emicizumab – can prevent bleeding in people with haemophilia A of 12 years of age and older who have inhibitors against factor eight. The main objective of this study was to compare emicizumab prophylaxis with on-demand bypassing agents. This study also compared emicizumab prophylaxis with the treatment participants were previously taking, and looked at whether there are any side effects of taking emicizumab, although these were not the main objectives of this study (for more information, please read the section entitled "What did doctors want to find out?").

What was the study medicine?

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

- You say this as 'em – me – sih – zuh – mab'.
- Emicizumab works by acting on proteins found in the blood to replace the function of the missing or inactive factor eight – this leads to blood clotting.
- The proteins that emicizumab acts on are other clotting factors, not factor eight itself.
- Emicizumab improves the ability of the blood to make clots and means that bleeding is less likely in people with haemophilia A.
- Emicizumab is a preventative (prophylactic) treatment. This means that it is given on a regular basis to prevent bleeding.
- Emicizumab is given as an injection under the skin. This is different from replacement factor eight treatment, which is given as an injection into a vein.

What did doctors want to find out?

Doctors did this study to see:

- If emicizumab can prevent bleeding in people with haemophilia A with inhibitors against factor eight compared with no preventative treatment (meaning people didn't take emicizumab or any other preventative treatment - see section 4 "What were the results from the main analysis of this study?").
- How well emicizumab prevents bleeding in people with haemophilia A with inhibitors against factor eight, compared with previous preventative (prophylactic) treatment in the same person. The previous preventative treatments were bypassing agents. To do this, doctors did a **previous** study that looked at people with haemophilia A with inhibitors against factor eight taking preventative (prophylactic) bypassing agents and recorded the number of bleeds they had. Twenty-four people from this previous study switched to preventative (prophylactic) emicizumab treatment in the HAVEN 1 study. The number of bleeds these 24 people had while taking emicizumab was compared with the number of bleeds they had when they were taking preventative (prophylactic) bypassing agents (see section 3 "What happened during this study?").
- How safe emicizumab is when given to people with haemophilia A with inhibitors against factor eight once every week. The doctors checked how many people had side effects when taking emicizumab during this study and what these side effects were (see section 5 "What side effects related to the study medicine were reported in the main analysis of this study?").

What kind of study was this?

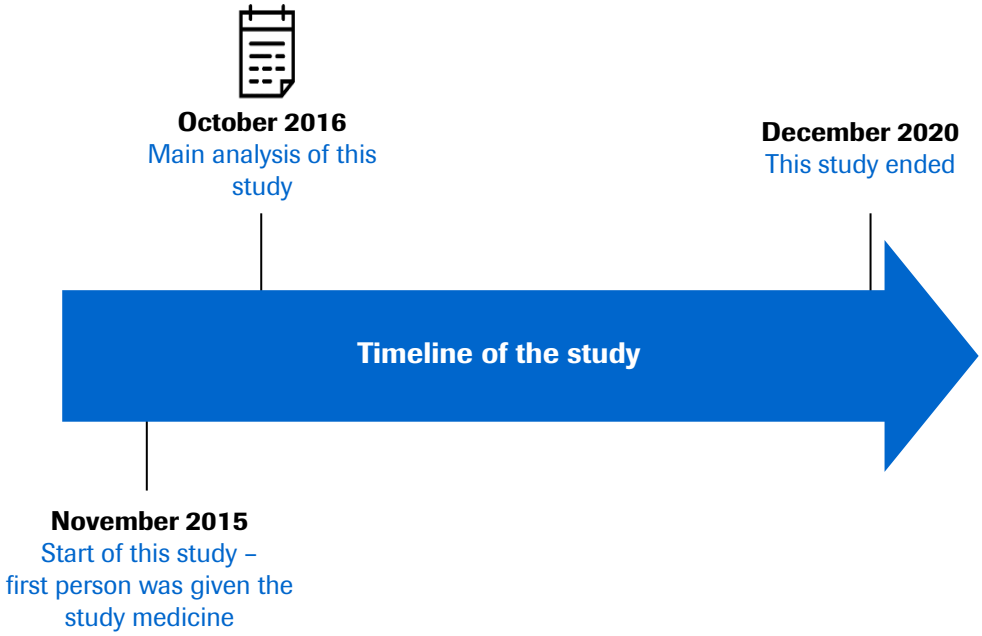
Emicizumab had previously been tested in smaller **Phase 1** and **Phase 2** studies. This was a larger **Phase 3** study. If a new drug is shown to be effective and has a favourable **safety profile** in a Phase 3 study, the results can be used to gain approval from health authorities in different countries to make the drug available to people with haemophilia A. Please see the glossary for full explanations of Phase 1, Phase 2 and Phase 3 studies.

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

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

When and where did this study take place?

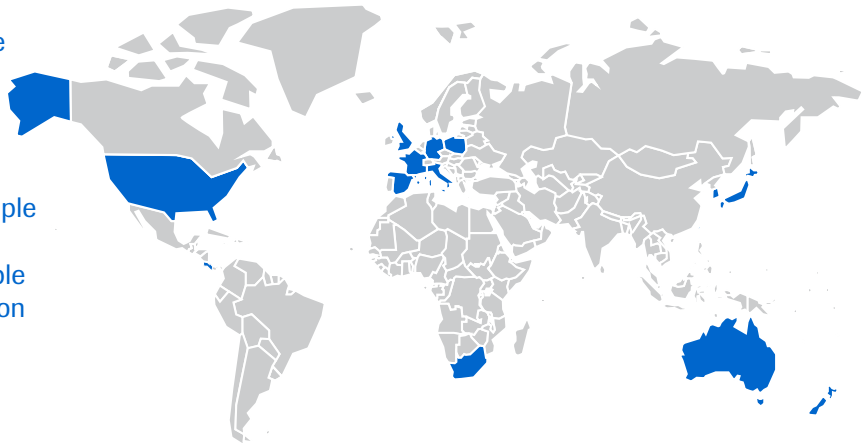
This study started in November 2015 and ended in December 2020. This summary focuses on the results of the main analysis, up until October 2016 – nearly a year after the start of the study. At the time of writing this summary, people were no longer taking part in the study since it has now been completed.



The calendar symbol on the timeline (📅) shows when the results in this summary were collected – October 2016.

The study took place at 43 study centres, across 14 countries around the world.
The following map shows the countries where this study took place.

- Australia – 4 people
- Costa Rica – 5 people
- France – 7 people
- Germany – 6 people
- Italy – 6 people
- Japan – 12 people
- New Zealand – 2 people
- Poland – 9 people
- South Africa – 6 people
- South Korea – 1 person
- Spain – 6 people
- Taiwan – 4 people
- UK – 5 people
- US – 36 people



2. Who took part in this study?

In this study, 109 people (including 24 people from the previous study) with haemophilia A (of any severity) with inhibitors against factor eight took part. They were all males, aged 12 years or older.

People could take part in this study if they:

- were aged 12 years or older
- had haemophilia A (mild, moderate or severe) with **inhibitors against factor eight**
- had been taking a bypassing agent to treat their haemophilia A.

People could not take part in this study if they:

- were taking – or planned to take – preventative (prophylactic) replacement factor eight during the study
- 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 happened during this study?

People who were taking on-demand bypassing agents before the start of this study were assigned by chance (**randomised**) to one of two treatment groups – Group A or Group B. People who were taking preventative (prophylactic) bypassing agents before the start of this study were assigned to Group C. People who were taking on-demand or preventative (prophylactic) bypassing agents and were being observed in a previous study, were assigned to Group D after enrolment for Groups A, B and C had closed. During this study, people were given emicizumab as an injection underneath the skin.

The treatment groups were:

- **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**'.

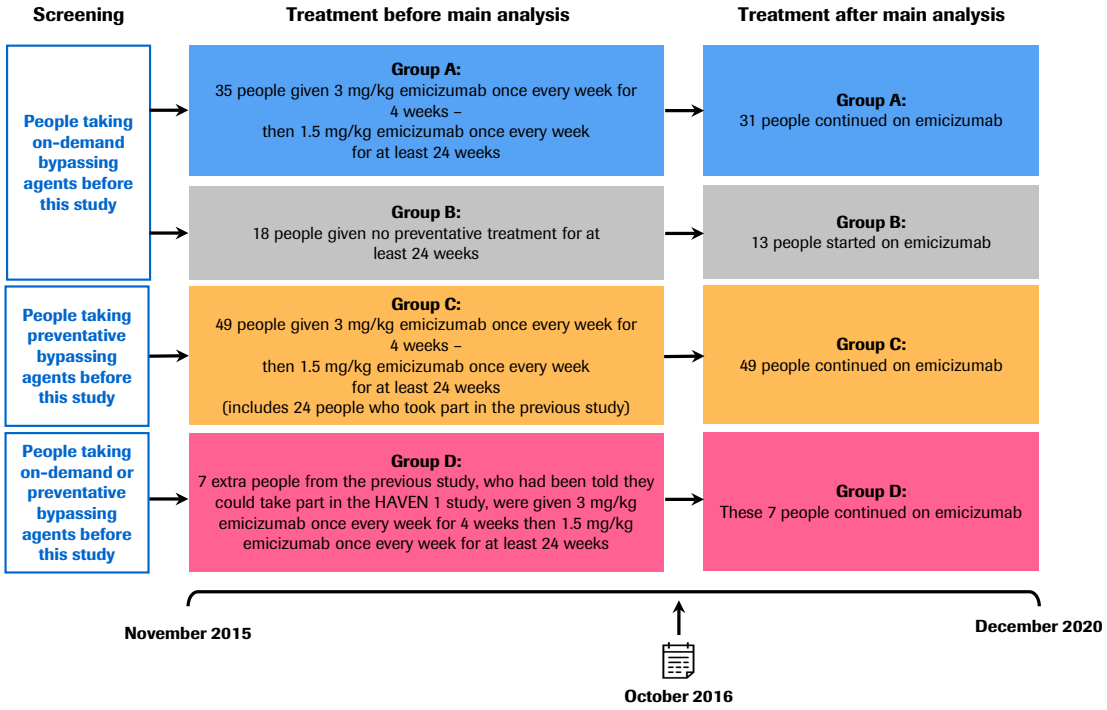
- **Group B** – these people did not receive emicizumab (or any preventative treatment) for the first 24 weeks of this study. After the main analysis (after 24 weeks), the people in Group B could start taking emicizumab. As in Group A, these people were first given loading doses of 3 mg/kg emicizumab once every week for four weeks. After four weeks, they started taking maintenance doses of 1.5 mg/kg emicizumab once every week for at least 24 weeks.

- **Group C** – 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 1.5 mg/kg emicizumab once every week for at least 24 weeks.

- **Group D** – 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 1.5 mg/kg emicizumab once every week for at least 24 weeks.

Everyone in the study could receive 'on-demand' bypassing agents if they had to treat a bleed.

The following image shows the study design:



The calendar symbol on the picture (📅) shows when the main analysis results in this summary were collected – October 2016.

After the main analysis at 24 weeks, people taking part in the study could either continue to take emicizumab or change to a different treatment if they preferred. Of those who did not receive any preventative treatment in group B, 13 out of 18 people chose to begin treatment with emicizumab after 24 weeks.

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

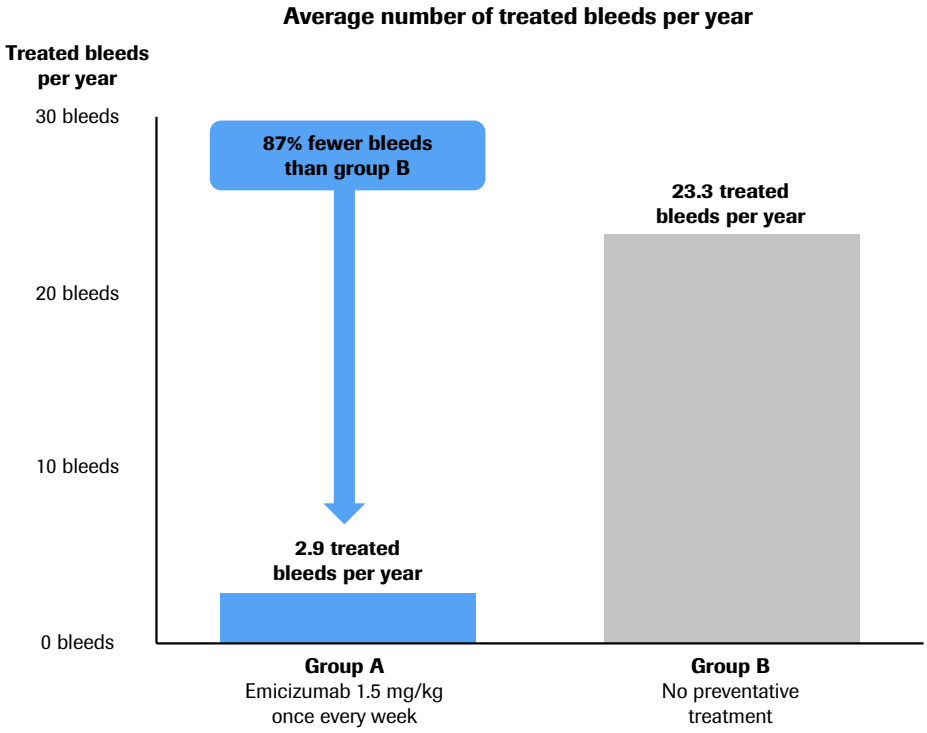
Question 1: How many bleeds did people have when given emicizumab once every week compared with no preventative treatment (on-demand treatment only)?

If a person had a bleed while taking part in the study, they could treat the bleed with a bypassing agent. Bleeds treated in this way are called '**treated bleeds**'.

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

People in Group A, who were given emicizumab once every week, had on average 2.9 treated bleeds per year. Almost two thirds of them (22 out of 35 people, 63%) had no treated bleeds. Most of the people in Group A (88.6%) had severe haemophilia A. The final results are consistent with those from the main analysis.

People in Group B, who were not receiving preventative treatment for the first 24 weeks, had on average 23.3 treated bleeds per year. Most of the people in Group B (17 out of 18, 94%) had at least one treated bleed. All of the people in Group B (100%) had severe haemophilia A.

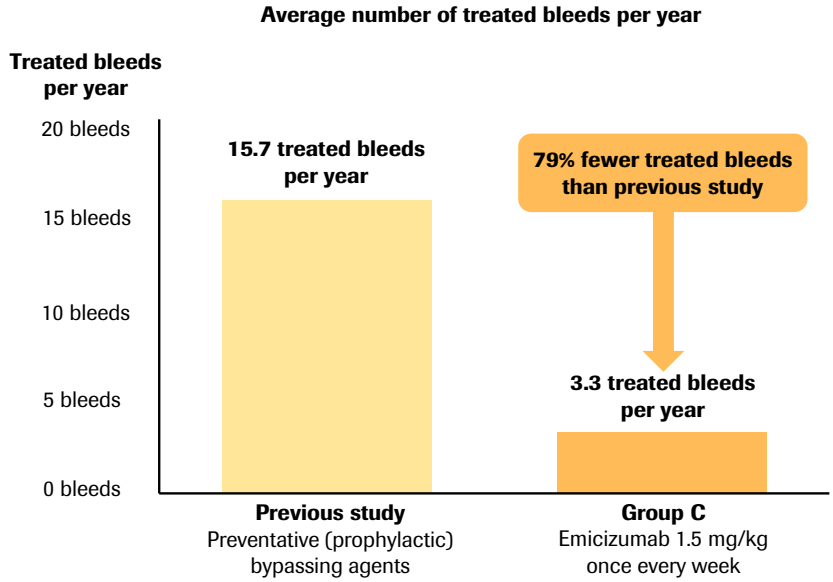


Question 2: How many bleeds did people have in this study compared with the number of bleeds they had when they were taking preventative (prophylactic) bypassing agents in the previous study?

Doctors also looked at how many treated bleeds 24 people taking emicizumab in this study had compared with how many treated bleeds the same 24 people had when they were taking preventative (prophylactic) bypassing agents in the previous study.

These 24 people had, on average, 3.3 treated bleeds per year when they were taking emicizumab in this study compared with an average of 15.7 treated bleeds per year when they were taking preventative (prophylactic) bypassing agents in the previous study.

This means that they had 79% fewer treated bleeds when they were taking emicizumab once every week than they did when they were taking preventative (prophylactic) bypassing agents.



Overall, there were 49 people in Group C who were given emicizumab once every week, and they had, on average, 5.1 treated bleeds per year. More than two thirds of them (34 out of 49 people, 69%) had no treated bleeds. Most of the people in Group C (95.9%) had severe haemophilia A. The final results are consistent with those from the main analysis.

The seven people in Group D joined the study after it had already started, meaning not enough results had been collected at the time of the main analysis. A further four patients are included in Group D for the final analysis, taking the total number of patients up to 11. On average, this group had 1.5 bleeds per year. This summary focuses on the key results from the study up to October 2016. 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 3: 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. Side effects that were not related to emicizumab treatment are not listed in this document.
- Not all of the people in this study had side effects.
- Side effects can vary from mild to serious and may vary from person to person.
- It is important to be aware that the side effects reported here may be different from those seen in other studies, or those that appear on the medicine leaflet.
- People of Groups A, B, C and D who received emicizumab treatment are included in the main safety results. The safety results for a total of 103 people are available.

For Group B, only people who had started to take emicizumab after at least 24 weeks on the study are included in this section.

Serious side effects

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

Up to the time of the main analysis, four people had experienced a **serious side effect** related to emicizumab treatment. These serious side effects were:

- Very small – also called microscopic – blood clots. These blood clots are called **thrombotic microangiopathies** or **TMAs**. One person in Group A and one person in Group C had this side effect.
- A blood clot in specific veins behind the eyes called the cavernous sinuses. This side effect is called **cavernous sinus thrombosis** and happened in one person in Group C.
- A blood clot below the surface of the skin called **thrombophlebitis superficial**, and death of the skin cells called **skin necrosis**. One person in Group A had these side effects.

The four people who had serious side effects related to emicizumab were also taking an on-demand bypassing agent called **activated prothrombin complex concentrate**. For all of the serious side effects reported, this bypassing agent had been taken repeatedly to reach a certain dose level and kept at that dose for more than one day.

After the main analysis date of this study (October 2016), one person taking emicizumab and **activated prothrombin complex concentrate** to treat rectal bleeding had a serious side effect of **thrombotic microangiopathy** and later died. The doctor looking after this person said that the thrombotic microangiopathy was resolving when the person died. The cause of death was the rectal bleeding, which was considered not to be related to emicizumab.

After the main analysis, the study sponsors gave instructions about how to use this bypassing agent more safely in people taking emicizumab. No other serious side effects related to emicizumab treatment were seen in this study up to the final analysis.

Common side effects

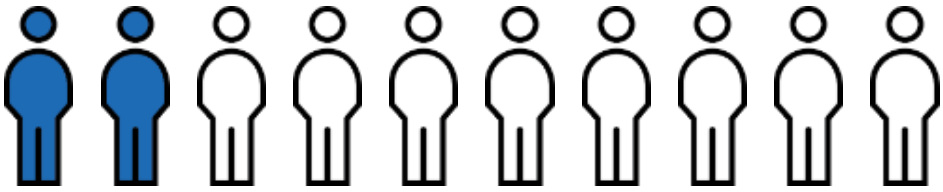
Side effects are considered '**common**' if they are seen in more than 5% of people (1 out of 20) in all treatment groups.

Up to the time of the main analysis, approximately two in ten people (22%) across Groups A, B, C and D 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 two days, and no treatment is needed. A side effect is considered '**moderate**' if it causes mild to moderate limitations on the person's activity, may cause the person to need some assistance, and little or no treatment is needed.

How many people had side effects related to emicizumab treatment?

23 out of 103 people



Around 2 in every 10 people (22%) had a side effect related to emicizumab

Most of these side effects were redness of the skin where the injection was given. This is called an '**injection-site reaction**'. In the majority of people who had injection-site reactions, symptoms were considered mild.

Tiredness and unusual hair growth were the only other 'common' side effects related to emicizumab seen up to the time of the main analysis. Similar common side effects were observed in the final analysis.

Other side effects

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

Side effect	Group A (34 people)	Group B (13 people)	Group C (49 people)	Group D (7 people)	All groups (103 people)
Injection-site reaction	7	1	3	0	11
Unusual hair growth	3	0	0	0	3
Tiredness (fatigue)	2	0	0	0	2
Small/microscopic clots (thrombotic microangiopathy)	1	0	1	0	2
General poor health	0	0	1	0	1
Sore on the skin	0	0	1	0	1
Dead skin cells (skin necrosis)	1	0	0	0	1
Pain in the stomach area	0	0	1	0	1
Feeling sick (nausea)	0	0	1	0	1
Blood clot in the cavernous sinuses (cavernous sinus thrombosis)	0	0	1	0	1
Loss of appetite	1	0	0	0	1
Thirst (dehydration)	1	0	0	0	1
Sore throat	1	0	0	0	1
Blood clot below the surface of the skin (thrombophlebitis superficial)	1	0	0	0	1

The side effects listed here for the main analysis are consistent with those observed in the final analysis. You can find information about other side effects that were not related to emicizumab (not shown here) on the websites listed at the end of this summary (see section 8 “Where can I find more information?”).

6. How has this study helped research?

The results presented here are from a single study of a total of 109 people aged 12 years and older with haemophilia A with inhibitors against factor eight. The results are helping doctors to learn more about the effect of emicizumab in people with haemophilia A with inhibitors against factor eight.

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

The results from this study show that, in people with haemophilia A with inhibitors against factor eight, emicizumab given once every week better prevented bleeding than no preventative (on-demand) treatment. It also gave better bleeding prevention than preventative (prophylactic) bypassing agents for those people who had taken part in the previous study. The results also show that emicizumab was well tolerated in most people enrolled in the study as less than one quarter (22%) had a side effect related to emicizumab treatment. Emicizumab caused serious side effects in four people when taken with a bypassing agent called **activated prothrombin complex concentrate**. For all of the serious side effects reported, this bypassing agent had been taken repeatedly to reach a certain dose level and kept at that dose for more than one day. One person taking emicizumab and activated prothrombin complex concentrate died because of a serious bleed during the study, but their doctor thought that their death was not related to either treatment. After the main analysis, the study sponsors gave instructions about how to use this bypassing agent more safely in people taking emicizumab and no more serious side effects related to emicizumab were seen up to the final analysis.

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

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

7. Are there plans for other studies?

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

8. Where can I find more information?

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

- https://clinicaltrials.gov/ct2/show/NCT02622321
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002866-21/results

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 Hemophilia A with Inhibitors”. The authors of the scientific paper are: Johannes Oldenburg, Johnny N. Mahlangu, Benjamin Kim, Christophe Schmitt, Michael U. Callaghan and others. The paper is published in ‘The New England Journal of Medicine’, volume number 377, on pages 809–818.

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 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Haemophilia A Participants with Inhibitors (HAVEN 1)”.

The study is known as ‘HAVEN 1’.

- The protocol number for this study is: BH29884.
- The ClinicalTrials.gov identifier for this study is: NCT02622321.
- The EudraCT number for this study is: 2015-002866-21.

9. Infographic summary

A study looking at whether emicizumab▼ can prevent bleeding in people with haemophilia A with inhibitors against factor eight who are aged 12 years and older – and whether there are any side effects of taking emicizumab

This is a summary of the results of a study, written for the general public and the people taking part. This study started in November 2015 and finished in December 2020. This summary focuses on the published results up until October 2016, when the main analysis took place.

Why was this study done?

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

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

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

A medicine called **emicizumab** was the focus of this study. Doctors did this study to see if emicizumab given once every week can prevent bleeding in people with haemophilia A with inhibitors against factor eight, and to look at whether there are any side effects of taking emicizumab.

Who took part in this study?

This study took place at:

43 centres across the world

14 countries around the world

109 people with haemophilia A took part.

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

What happened in this study?

- Those taking on-demand bypassing agents before the start of this study were assigned by chance to one of two treatment groups – Group A or Group B.
- Those taking preventative (prophylactic) bypassing agents before the start of this study were assigned to Group C (including 24 who took part in a previous study).
- Those taking on-demand or preventative (prophylactic) bypassing agents and were being observed in a previous study were assigned to Group D, after enrolment for Groups A, B and C had closed.

Group A
35 people
Emicizumab 3 mg/kg once every week for 4 weeks
then
Emicizumab 1.5 mg/kg once every week for at least 24 weeks

Group B
18 people
No preventative treatment for at least 24 weeks

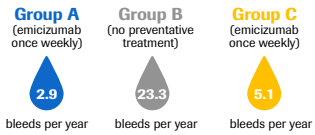
Group C
49 people
Emicizumab 3 mg/kg once every week for 4 weeks
then
Emicizumab 1.5 mg/kg once every week for at least 24 weeks

Group D
7 people
Emicizumab 3 mg/kg once every week for 4 weeks
then
Emicizumab 1.5 mg/kg once every week for at least 24 weeks

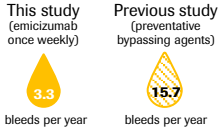
- If a person had a bleed while taking part in the study, they could treat the bleed with bypassing agents. Bleeds treated in this way are called 'treated bleeds'.
- Doctors looked at how many treated bleeds people had, on average, over the course of a year when taking emicizumab compared with no preventative treatment.
- Doctors also looked at how many treated bleeds 24 people taking emicizumab in this study had, compared with how many treated bleeds the same 24 people had when they were taking preventative (prophylactic) bypassing agents in the previous study.

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

People in **Group A and C who were taking emicizumab once every week had fewer treated bleeds** than people in Group B who received no preventative treatment.



Twenty-four people in **Group C had 79% fewer treated bleeds when they were taking emicizumab once every week** than they did when they were taking preventative (prophylactic) bypassing agents in the previous study.



The seven people in **Group D** joined the study after it had started, meaning not enough results had been collected at the time of the main analysis. A further four patients are included in Group D for the final analysis, taking the total number of patients up to 11. On average, this group had 1.5 bleeds per year.

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.

Common side effects

Around **2 in every 10 people (22%)** 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 main 'common' side effect related to emicizumab – the majority of symptoms were mild.

Serious side effects

Four people experienced a serious side effect related to emicizumab when also taking an on-demand bypassing agent called **activated prothrombin complex concentrate.***

This bypassing agent had been taken repeatedly to reach a certain dose level, and kept at that dose for more than one day. After the main analysis, the study sponsors gave instructions how to use this bypassing agent more safely in people taking emicizumab and no more serious side effects were reported up to the final analysis.

What did this study tell us?

Emicizumab given once every week in people with haemophilia A with inhibitors against factor eight helps to prevent bleeding. The results also show that emicizumab was well tolerated in most people enrolled in the study as less than one quarter (22%) had a side effect related to emicizumab treatment.
The final study results are similar to those of the main analysis.

This study is known as 'HAVEN 1' (NCT02622321) and was organised and paid for by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd.
Date of preparation: July 2021.

▼ 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 '**bypassing agents**', '**inhibitors against factor eight**', '**replacement factor eight**', '**side effects**' and '**serious side effects**', please see the glossary section of the layperson summary.
*The four serious side effects reported included thrombotic microangiopathy, cavernous sinus thrombosis, thrombophlebitis superficial and skin necrosis; please see the full layperson summary for more information.

10. Glossary

Bypassing agents	Treatment given to people with haemophilia with inhibitors against factor eight. Instead of replacing the missing or inactive factor eight, bypassing agents go around (or bypass) it to help the blood clot.
Clinical trial	When researchers give a group of people a medicine to find out more information about how the medicine works, if it helps to improve people's condition, and if it causes any side effects. The researchers regularly follow-up with the people taking the medicine and perform medical tests.
Common side effect	A side effect that is seen in more than 5% of the people (1 out of 20).
DNA	DNA is the code that forms the building blocks of all known living organisms, from bacteria to humans. The DNA in our body carries the instructions to build us, and is the material that makes up our genes.
Gene	Genes are units of DNA inherited from our parents that contain all the information needed to make people who they are – from the colour of someone's eyes to their blood type.
Inherited	Passed on from one generation to the next through certain genes.
Inhibitors against factor eight	Antibodies produced as a reaction by the body's immune system in response to treatment with replacement factor eight. Inhibitors against factor eight can stop replacement factor eight treatment from working to prevent bleeds. Inhibitors against factor eight often develop at a young age when children are first treated with replacement factor eight.
Injection-site reaction	Redness, pain or swelling of the skin at the site where an injection was given.
IV injection	Intravenous injection. An injection into a vein.
Loading dose	An initial higher dose of a medicine that may be given at the beginning of a course of treatment to increase levels of the medicine in the blood quickly before dropping to a lower maintenance dose of that same medicine.
Maintenance dose	The amount of medication given to maintain a level of the medicine in the blood that offers acceptable bleed protection.
Mild side effect	A side effect that causes mild discomfort, lasts for less than two days, and does not need any treatment.

Moderate side effect	A side effect that causes mild to moderate limitation in activity, may cause the person to need some assistance, and needs little or no treatment.
On-demand treatment	Treatment given after a bleed has happened to help the bleeding stop.
Open-label	A clinical trial where both the researchers and the people taking part know which of the study medicines people are taking.
Phase 1 study	One of the first clinical trials investigating a new medicine. Study doctors give the new medicine to a small number of people, to look at how it affects them and find out more about the medicine.
Phase 2 study	A clinical trial to look at how effective a new medicine is in people with the disease or condition being studied, and to determine what the side effects of the new medicine are. Phase 2 studies involve more people and usually last longer than Phase 1 studies.
Phase 3 study	A clinical trial to further evaluate how effective and safe the new medicine is, usually involving more people than Phase 1 and 2 trials. Phase 3 trials may also compare a new medicine with an existing treatment option to show which medicine works better (the new medicine or the old one), what the side effects of the new medicine are, and how the new treatment affects people's quality of life.
Prophylactic treatment	Treatment given on a regular basis to prevent bleeding and subsequent joint and muscle damage.
Protein	A long chain of very small units in our body called amino acids that are organised into both simple and complex structures, and form almost everything in a living organism, from hair and skin to enzymes and antibodies. Information on how to build proteins is found in the genes.
Randomised	A trial in which people are split into groups at random. This is usually done by a computer. Typically, each group will be given a different type of treatment.
Replacement factor eight	Factor eight treatment given to replace the missing or inactive factor eight in people with haemophilia A. This 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.