Clinical Trial Results – Layperson Summary

A study looking at whether emicizumab can prevent bleeding in children with haemophilia A with inhibitors against factor eight – 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 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
- caregivers of the children who took part in this study.

This study started in July 2016 and finished in November 2020. This summary includes the results up until April 2018 when the main analysis took place. More information may now be known.

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 the summary

Thank you to the children who took part in this study

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

1. General information about this study

Why was this study done?

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.

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 children taking part in this study have **inhibitors against factor eight**.

This study was done to see whether a medicine – emicizumab – can prevent bleeding in children with haemophilia A with inhibitors against factor eight. This study also compared

emicizumab with the treatment the children with haemophilia A with inhibitors against factor eight were previously taking, and looked at whether there are any side effects of taking emicizumab.

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 clotting factor proteins found in the blood (not factor eight) to replace the function of the missing or inactive factor eight.
- This improves the ability of the blood to make clots and means that bleeding is less likely in people with haemophilia A.
- Emicizumab is a preventative (prophylactic) treatment. This means that it is given on a regular basis to prevent bleeding.
- Emicizumab is given as an injection under the skin. This is different than replacement factor eight treatment, which is given as an injection into a vein.

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

What did doctors want to find out?

Doctors did this study to see if emicizumab can prevent bleeding in children with haemophilia A with inhibitors against factor eight (see section 4 "What were the results from the main analysis of this study?").

They also wanted to see how well emicizumab prevents bleeding in children with haemophilia A with inhibitors against factor eight, compared with previous preventative (prophylactic) treatment in the same children. The previous preventative treatments were bypassing agents. To do this, doctors did a previous study that looked at children with haemophilia A with inhibitors against factor eight taking preventative (prophylactic) bypassing agents and recorded the number of bleeds they had. In this study, 15 of these same children then switched to preventative (prophylactic) emicizumab treatment. The number of bleeds these 15 children had while taking emicizumab was compared with the number of bleeds they had when they were taking preventative (prophylactic) bypassing agents.

Doctors also wanted to find out how safe emicizumab is when given to children with haemophilia A with inhibitors against factor eight once every week, once every two weeks, or once every four weeks. The doctors checked how many children 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?").

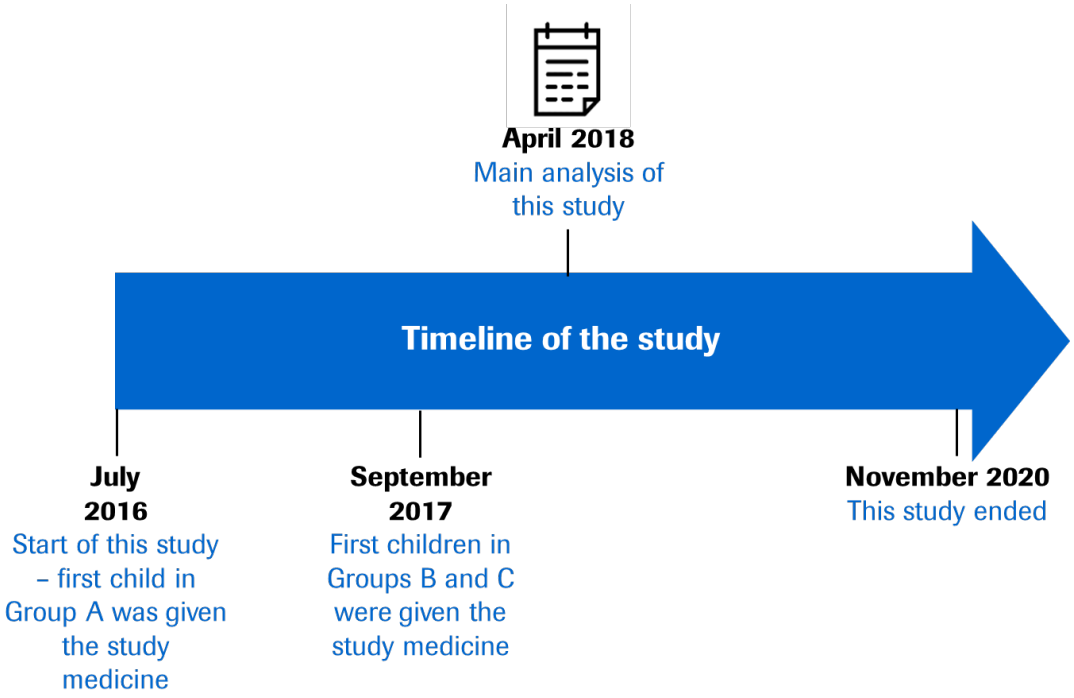
What kind of study was this?

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

When and where did this study take place?

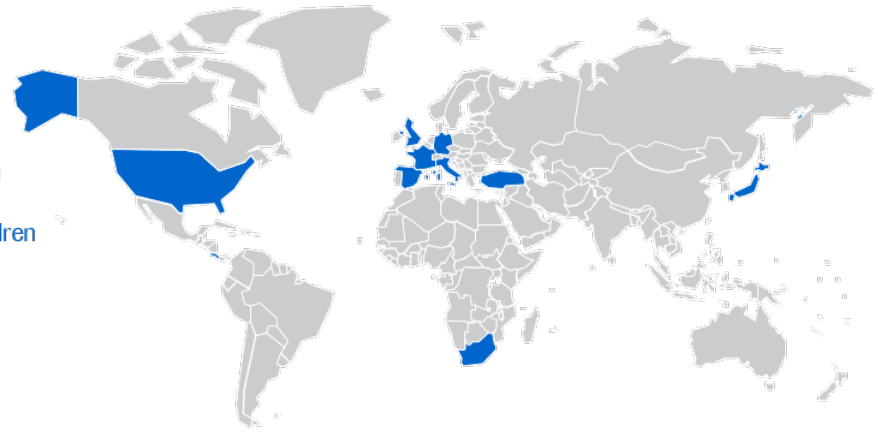
This study started in July 2016 and ended in November 2020. This summary includes the results from the main analysis that were collected and analysed in April 2018. The timeline of the study shows when the first children in each treatment group (A, B or C) were given emicizumab (see section 3 "What happened during this study?" for more information on the treatment groups).



The calendar symbol on the timeline (📅) shows when the results in this summary were collected – April 2018.

This study took place at 27 study centres, across 10 countries around the world. The following map shows the countries where this study took place.

- US – 24 children
- Spain – 12 children
- UK – 10 children
- Japan – 9 children
- Turkey – 8 children
- Germany – 7 children
- Itay – 7 children
- South Africa – 6 children
- France – 4 children
- Costa Rica – 1 child



2. Who took part in this study?

In this study, 88 children with haemophilia A with inhibitors against factor eight took part. They were aged between 1 and 15 years old, and were all boys.

Children could take part in this study if they:

- were younger than 12 years old (or between the ages of 12 and 17 and weighed less than 40 kilograms at the start of the study)
- had haemophilia A **with inhibitors against factor eight**
- had been taking a bypassing agent to treat their haemophilia A.

Children 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?

During this study, children were given emicizumab as an injection underneath the skin at one of three doses.

The treatment groups were:

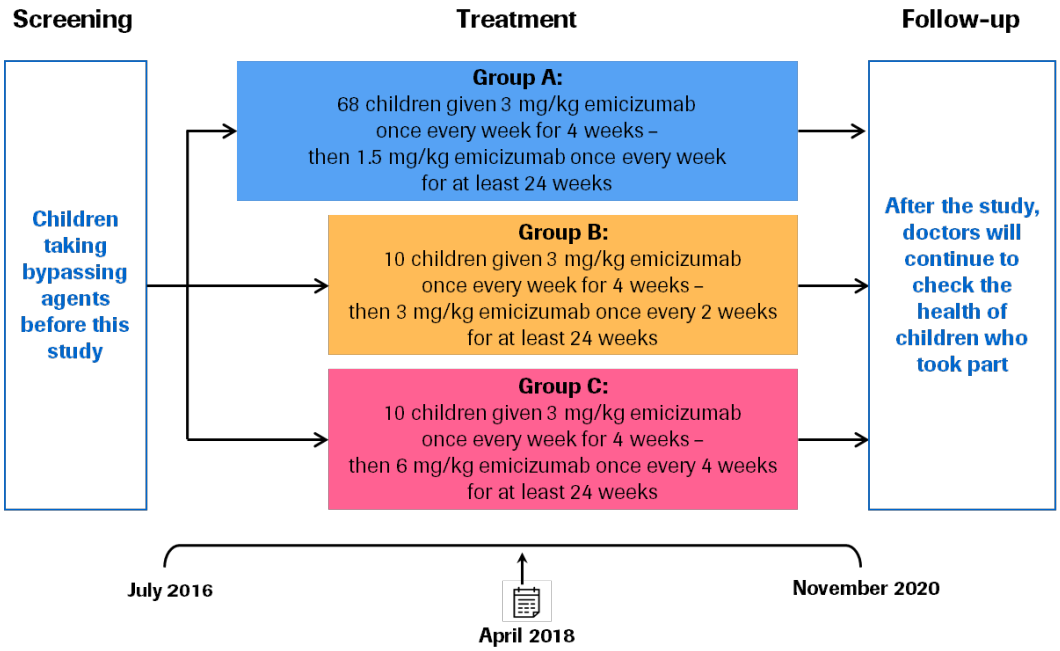
- **Group A** – to quickly increase the amount of emicizumab in their blood, these children were first given 3 mg/kg emicizumab (meaning three milligrams of emicizumab for every one kilogram of body weight) once every week for four weeks. These are called the '**loading doses**'. After four weeks, they 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 children 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** – as in Groups A and B, these children 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 6 mg/kg emicizumab once every four weeks for at least 24 weeks.

Every child in this study could receive 'on-demand' bypassing agents if they had a bleed.

The following image shows the study design:



When this study finished, children taking part could either continue to take emicizumab, or change to a different treatment if they preferred.

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

Question 1: How many bleeds did children have when given emicizumab once every week, once every two weeks, or once every four weeks?

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

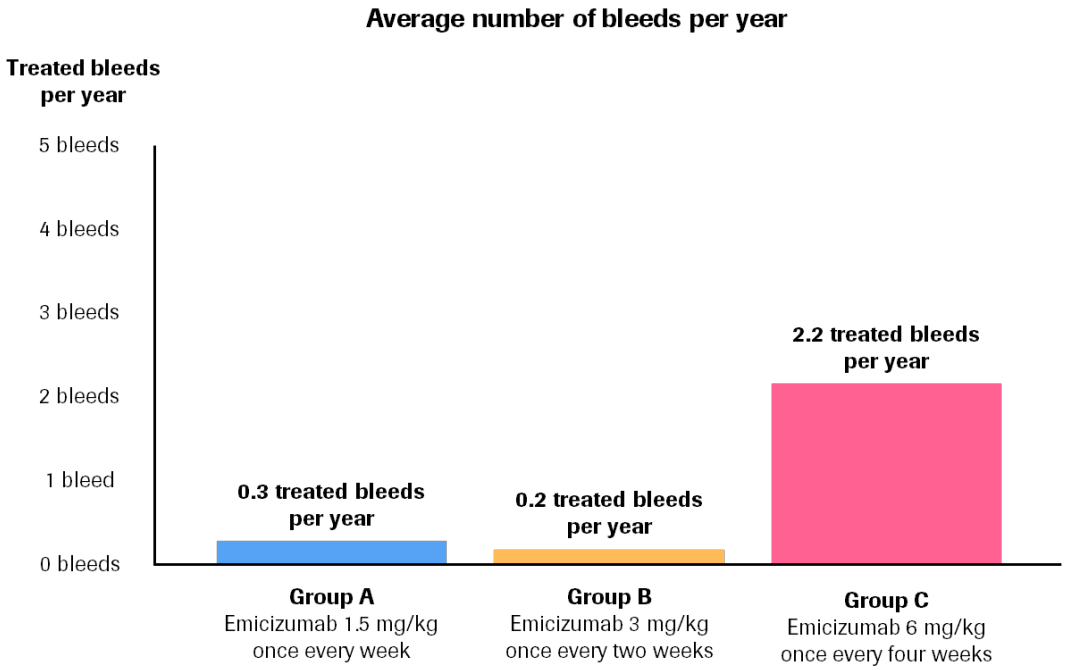
Doctors looked at how many treated bleeds children had on average over the course of a year, when taking emicizumab to prevent bleeding. At the time of the main analysis, some children in this study had not been treated for a full year. If this was the case, doctors used the numbers of treated bleeds children had during the time they received treatment, and estimated how many treated bleeds that child could potentially have over the course of a year.

Only children who were younger than 12 years old are included in these results (a total of 85 children), because the main aim of this study was to look at emicizumab in children younger than 12 years of age. Three children were older than 12 years of age but weighed less than 40 kilograms at the start of the study and were not included in these results.

Children in Group A were given emicizumab once every week. Most of the children in Group A (50 out of 65 children, 77%) had no treated bleeds. Children in Group A had on average less than one treated bleed per year. All of these children (65 out of 65 children, 100%) had between zero and three treated bleeds while they were taking emicizumab.

Children in Group B were given emicizumab once every two weeks. Most of the children in Group B (9 out of 10 children, 90%) had no treated bleeds. Children in Group B had on average less than one treated bleed per year. All of these children (10 out of 10 children, 100%) had between zero and three treated bleeds while they were taking emicizumab.

Children in Group C were given emicizumab once every four weeks. Six out of ten children (60%) in Group C had no treated bleeds. Children in Group C had on average two treated bleeds per year. All of these children (10 out of 10 children, 100%) had between zero and three treated bleeds while they were taking emicizumab.



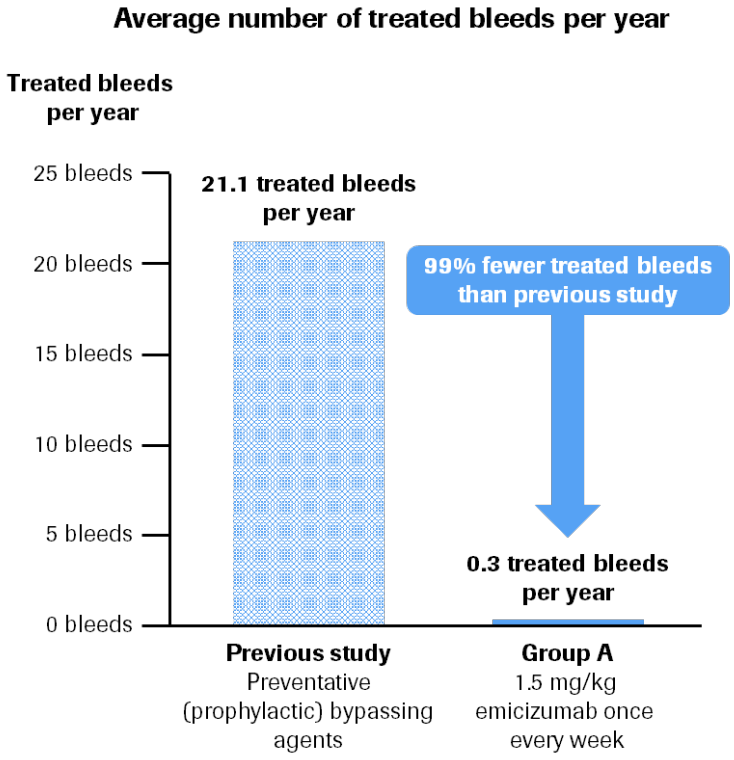
Although the average number of treated bleeds per year was higher in Group C compared with Groups A or B, this was mostly caused by two children in Group C having many bleeds. In one of these two children, emicizumab stopped working. Study doctors believed that all three doses (emicizumab given once every week, once every two weeks and once every four weeks) were effective at preventing bleeding.

Question 2: How many bleeds did children 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 children taking emicizumab in this study had compared with how many treated bleeds the same children had when they were taking preventative (prophylactic) bypassing agents in the previous study. They did this by looking at 15 children from Group A. Preventative (prophylactic) bypassing agents have limitations and do not always protect against bleeds in all people with haemophilia A with inhibitors against factor eight.

These 15 children had, on average, 0.3 treated bleeds per year when they were taking emicizumab in this study compared with an average of 21.1 treated bleeds per year when they were taking preventative (prophylactic) bypassing agents in the previous study.

This means that they had 99% fewer treated bleeds when they were taking emicizumab once every week than they did when they were taking preventative (prophylactic) bypassing agents.



This section only shows the key results from this study up to April 2018. 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 children had side effects related to emicizumab?

Side effects (also known as 'adverse reactions') are unwanted medical problems (such as feeling dizzy) that happen during the study.

- They are described in this summary because the study doctors believe the described side effects were related to emicizumab treatment.
- Not all of the children in this study had side effects.
- Side effects can vary from mild to serious and may vary from child to child.
- 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.
- The following sections talk about the serious and common 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.

Serious side effects

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

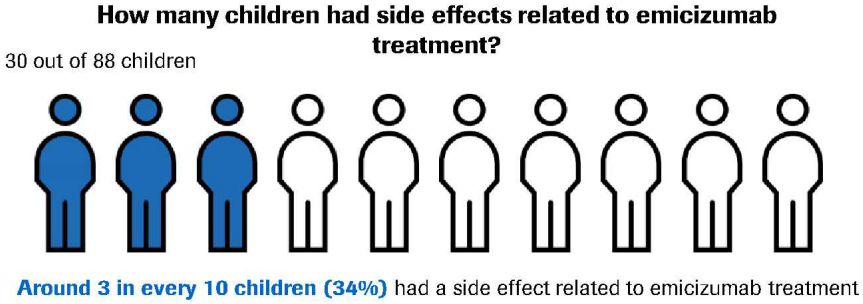
During this study, 1 out of 88 children (about 1%) had a **serious side effect** related to emicizumab treatment, which was that emicizumab stopped working.

This child and his family decided that he should stop taking emicizumab because of this side effect. No other children in this study stopped taking emicizumab. No other serious side effects related to emicizumab treatment were seen in this study.

Common side effects

During this study, approximately one in three children (34%) had a side effect related to emicizumab 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 child's activity, may cause the child to need some assistance, and little or no treatment is needed.



Most of these side effects were redness of the skin where the injection was given. This is called an '**injection site reaction**'. In 25 out of the 27 children who had injection site reactions (93%), these reactions were mild. In two children (7%), these reactions were moderate.

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

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

Other side effects

This table lists all the side effects in this study that the doctors believed to be related to emicizumab. It also shows the number of children in Groups A, B, and C who had each of these side effects.

Side effects	Group A (68 children)	Group B (10 children)	Group C (10 children)	All groups (88 children)
Injection site reaction	18	2	7	27
Blood type could not be determined	1	1	1	3
Increased number of a type of white blood cell	1	0	0	1
Emicizumab stopped working	0	0	1	1
Bruising	1	0	0	1
Rash	1	0	0	1
Feeling sick (nausea)	1	0	0	1
Cough	1	0	0	1

You can find information about other side effects that were unrelated 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 88 children with haemophilia A with inhibitors against factor eight. The results are helping doctors to learn more about the effect of emicizumab in children with haemophilia A with inhibitors against factor eight.

Previous studies have shown that emicizumab helps to prevent bleeding in adults with haemophilia A with and without factor eight inhibitors when given once every week, once every two weeks, or once every four weeks.

The results from this study show that emicizumab given once every week, once every two weeks or once every four weeks helps to prevent bleeding in children with haemophilia A with inhibitors against factor eight. Approximately one in three children with haemophilia A with inhibitors against factor eight had side effects related to emicizumab that were not considered serious. One child had a serious side effect that was related to emicizumab (emicizumab stopped working).

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/results/NCT02795767
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000073-21/results

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: "A multicentre, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors". The authors of the scientific paper are: Guy Young, Ri Liesner, Tiffany Chang, Robert Sidonio Jr, Johannes Oldenburg and others. The paper is published in the journal 'Blood', volume number 134, on pages 2127–2138.

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 this study and other identifying information

The full title of this study is: "A multicentre, open-label, phase III clinical trial to evaluate the efficacy, safety and pharmacokinetics of subcutaneous administration of emicizumab in haemophilia A paediatric patients with inhibitors".

This study is known as 'HAVEN 2'.

- The protocol number for this study is: BH29992.
- The ClinicalTrials.gov identifier for this study is: NCT02795767.
- The EudraCT number for this study is: 2016-000073-21.

9. Infographic summary

A study looking at whether emicizumab can prevent bleeding in children with haemophilia A with inhibitors against factor eight – 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 caregivers of the children that took part. This study started in July 2016 and finished in November 2020. Here, we report the results from the main analysis of this study up until April 2018.

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 regularly can prevent bleeding in children 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:

27 centres across the world

10 countries around the world

88 children with haemophilia A with inhibitors against factor eight took part.

They were aged between 1 and 15 years old and were all boys.

What happened in this study?

The children were all previously taking preventative bypassing agents, which go around (or bypass) factor eight to prevent bleeds. During this study, they were given emicizumab at one of three doses.

Group A
68 children

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
10 children

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

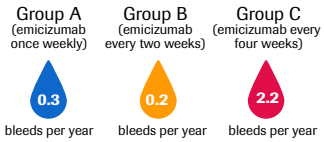
Group C
10 children

Emicizumab 3 mg/kg once every week for four weeks
then
Emicizumab 6.0 mg/kg once every four weeks for at least 24 weeks

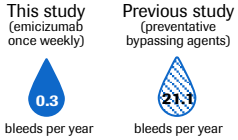
- If a child had a bleed while taking part in the study, they could treat the bleed with a bypassing agent. To see if emicizumab prevents bleeding, doctors looked at the number of treated bleeds children in Groups A, B and C had.
- Doctors also looked at how many treated bleeds 15 children in Group A had when they were taking emicizumab in this study compared with when they were previously receiving preventative bypassing agents.

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

Children taking emicizumab had **around zero to two treated bleeds per year.***



In **Group A**, 15 children had **99% fewer treated bleeds** when taking emicizumab than they did when they were taking preventative bypassing agents.



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.

One in three children (34%) had a side effect related to emicizumab treatment

Side effects are considered 'common' if they are seen in more than 5% of people (1 out of 20) in all treatment groups. Redness of the skin where the injection was given was the only 'common' side effect related to emicizumab seen during this study. It was not considered serious.

One child out of 88 had a serious side effect related to emicizumab, which was that emicizumab stopped working.

What did this study tell us?

Emicizumab given once every week, once every two weeks or once every four weeks helps to prevent bleeding in children with haemophilia A with inhibitors against factor eight. One in three children had side effects related to emicizumab. Emicizumab stopped working in one child, which was considered a serious side effect related to emicizumab.

This study is known as 'HAVEN 2' (NCT02795767) and was organised and paid for by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd.
M-XX-00012636 Date of preparation: March 2023.

For the definition of '**bypassing agents**', '**side effects**' and '**serious side effects**', please see the glossary section of the layperson summary. *Only children aged 12 years old or younger were included in the analysis to see if emicizumab can prevent bleeding (85 out of 88 children). This was because the aim of this study was to look at emicizumab in children younger than 12 years old.

10. Glossary

Blood type	There are four main blood types (A, B, O and AB). Your blood type is determined by the genes you inherit from your parents.
Bypassing agents	Treatment given to people with haemophilia with inhibitors against factor eight. Instead of replacing the missing or inactive factor eight, bypassing agents go around (or bypass) it to help the blood clot.
Clinical trial	When researchers give a group of people a medicine to find out more information about how the medicine works, if it helps to improve people's condition, and if it causes any side effects. The researchers regularly follow-up with the people taking the medicine and perform medical tests.
Common side effect	A side effect that is seen in more than 5% of people (1 out of 20).
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.
Replacement factor eight	Factor eight treatment given to replace the missing or inactive factor eight in people with haemophilia. This can be taken from human blood donations, or artificially created in a laboratory.

Safety profile	An overview of the characteristics of the medicine, including how it works, what it does, and any side effects.
Serious side effect	A side effect that is life-threatening, needs hospital care, causes lasting problems and severe limitation of activity, or causes death.
Side effect	An unwanted medical effect that is caused by taking a medicine. Side effects can be positive or negative.
Treated bleed	A bleed treated with replacement factor eight or bypassing agents.
White blood cells	Part of the body's immune system. They help the body fight infections and other diseases.