Clinical Trial Results – Layperson Summary

A study to look at how effective and safe emicizumab is at preventing bleeding in infants (children under 12 months old) with severe haemophilia A without inhibitors

See the end of the summary for the full title of the study, and a hyperlinked glossary of medical terms. Hyperlinked terms are in **bold and underlined**.

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
- the caregivers of the infants who took part in the study

The study started on February 4, 2021, and is expected to end in May 2030. This summary contains results from the main analysis, information was collected up until May 22, 2023 (when infants, i.e. children under 12 months old, had been receiving emicizumab for at least 52 weeks). At the time of writing this summary, the study is still happening – study doctors are still collecting information.

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

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

Contents of this summary

Thank you to the people who took part in this study

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

1. General information about this study

What is haemophilia A?

Haemophilia A is a rare **inherited** bleeding disorder caused by an abnormal **gene** on the **X chromosome** meaning mostly men and boys are affected. Females can also be affected by haemophilia A, but the way that genes work means that symptoms vary between people. Some females may have no symptoms, and some may have more serious bleeding symptoms, which can be like those experienced by males.

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 properly. This means that people with haemophilia A can have lots of bleeds that can last for a prolonged time, including in their joints and muscles. These bleeds can be caused by minor injuries and may have no obvious cause.

People with haemophilia A can be grouped by how severe their haemophilia A is, based on how little clotting factor eight they have. Infants in this study had **severe haemophilia A** meaning that they have less than 1% of the clotting factor eight activity of someone without haemophilia A.

How is haemophilia A treated?

Traditionally, one of the standard treatments for people with haemophilia A has been 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 clot. Replacement factor eight is injected into a vein (called an **'intravenous (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 preventive treatment is called **'prophylactic treatment'**.

When replacement factor eight is given to prevent bleeding, it is usually given twice a week; however, there are many types of replacement factor eight treatment, and different people may receive treatment more or less often than this or receive different doses of the treatment. This is because replacement factor eight remains in the blood for a short period of time – exactly how short depends on how it is processed by each person's body, and the type of replacement factor eight treatment given.

Some people with haemophilia A form **inhibitors against factor eight** that stop replacement factor eight treatment from working. Some of the infants in this study received replacement factor eight before the study, but none of them had formed inhibitors against factor eight at the start of the study.

Another standard treatment that people with haemophilia A can receive to prevent bleeding is called 'emicizumab'; this treatment works differently to replacement factor eight treatment. In addition to replacement factor eight and emicizumab, there are other treatments available for people with haemophilia A; however, emicizumab was the treatment given to infants taking part in this study.

What is the study medicine?

The study medicine, 'emicizumab' (HEMLIBRA®), is a type of treatment for haemophilia A, sometimes called **'factor eight mimicking antibody'**.

- You say this as 'em – me – sih – zuh – mab'.
- Emicizumab mimics the action of the factor eight protein, allowing the blood to form clots.
- Emicizumab is more stable than factor eight replacement treatment, meaning it stays in the body for longer.
- 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 preventive (prophylactic) treatment. This means that it is given on a regular basis to prevent bleeding.
- Emicizumab is given as an injection under the skin (known as a **'subcutaneous injection'**). This is different from replacement factor eight treatment, which is 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 works in people with haemophilia A with inhibitors against factor eight and people without inhibitors against factor eight and has been approved for use in people of all ages within these populations by the health authorities.

What are the challenges of treating infants with haemophilia A?

For infants (children under the age of 12 months), preventing bleeds is important, as bleeds that happen early in life can lead to complications and disability in adulthood, including problems in the joints.

When infants with haemophilia A do not receive preventive treatment, they are more at risk of life-threatening bleeds within the head (known as **'intracranial haemorrhage'**) compared with infants without haemophilia. There is a sizable risk of intracranial haemorrhage in the first 12 months of life in infants with haemophilia, and so delaying preventive treatment until infants are older than 12 months might increase their risk of intracranial haemorrhage.

Replacement factor eight used for preventive treatment requires frequent and long-term injection into veins. To help deliver replacement factor eight preventive treatment, young children often have **central venous access devices** inserted, which are put into a vein to give direct access to the bloodstream. These devices are designed to remain in the body for a long time and can sometimes stay inserted for more than a year. Use of central venous access devices presents a risk of **thrombosis** and infection due to microbes entering the blood through the break in the skin. Because of these risks, factor eight replacement treatment is often not started until children are older than 12 months so that the treatment can be delivered without the need for inserting a central venous access device.

As emicizumab is given through injection under the skin once every week at most, it is less of a burden to deliver to infants than frequent replacement factor eight given through injection into a vein. Therefore, preventive treatment with emicizumab can be given from birth, which might reduce risk of intracranial haemorrhages, as well as other bleeds that can lead to joint problems in adulthood. Emicizumab treatment also avoids the use of central venous access devices, reducing the risks associated with this, such as infections.

What did study doctors want to find out?

The doctors on the study looked at how many bleeds infants with haemophilia A without inhibitors against factor eight had when they received emicizumab once every week for the first 4 weeks of the study and, after this, once every 2 weeks for at least 48 weeks (see section 4 “How many bleeds did infants on the study experience?”).

The study also looked at side effects in infants who received emicizumab at the doses described above (see section 5 “What other results were reported in this study?”). It is important to continue to check the side effects of a medicine even after it is approved for doctors to give to patients.

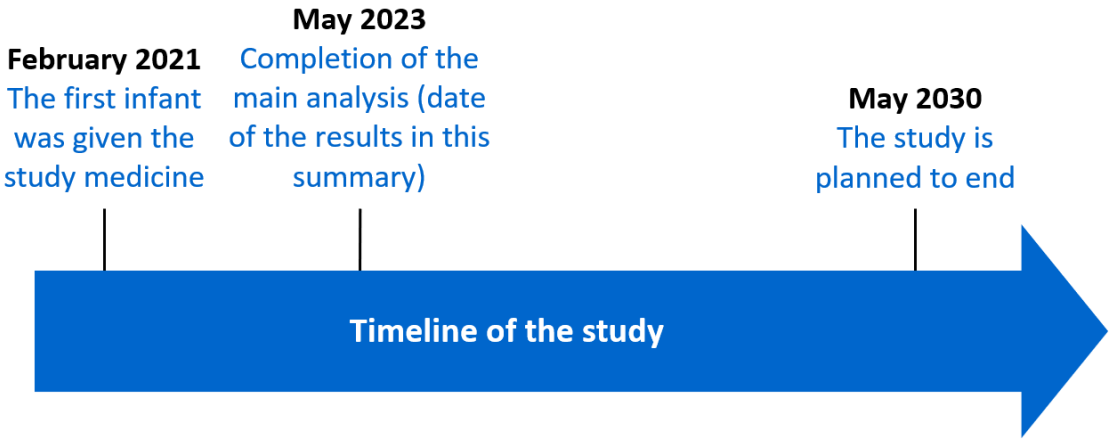
What kind of study was this?

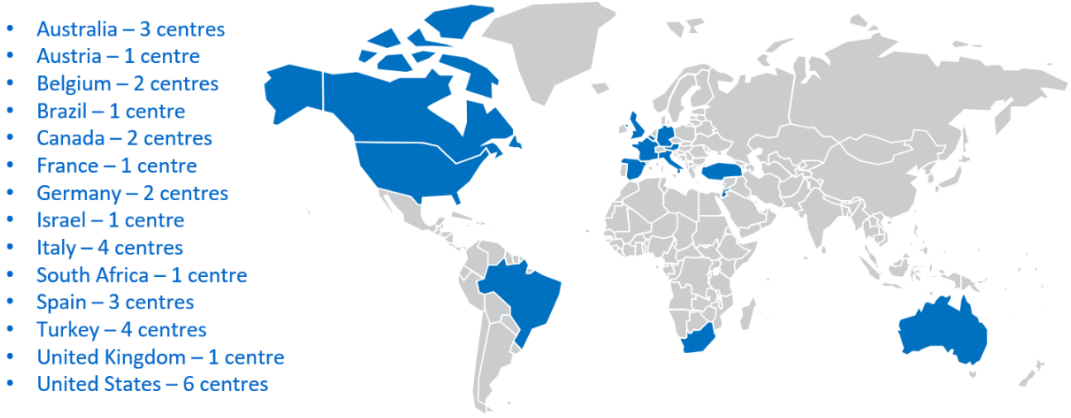
The HAVEN 7 trial is a **Phase 3b** study. This is a type of study that is carried out after a drug has been submitted for approval by the health authorities, usually to gain more information in a greater number of patients, either to support the approval or expand the evidence available after approval.

The study is an **open label** study. This means that both doctors and the caregivers of the children in the study were aware of the treatment being received.

When and where did this study take place?

This study started on February 4, 2021, and is expected to end in May 2030. This summary focuses on the results from the main analysis, up until May 22, 2023 – 52 weeks after the first person started the study. At the time of writing this summary, the study is still ongoing – study doctors are still collecting information and infants taking part in the study are being monitored.





This study took place at 32 study centres, which are medical facilities where clinical studies take place, across 14 countries. The map above shows the countries where the study took place.

2. Who is taking part in this study?

In the study, 55 infants with severe haemophilia A took part. They were all males and their ages at the start of the study ranged from 9 days old to 11 months and 30 days old: 25 of the infants were younger than 3 months old, and 30 were between 3 and 12 months old.

Infants could take part in the study if they:

- were 12 months old or younger at the time they joined the study
- weighed 3 kg or more
- had not previously received any haemophilia treatment (defined as **'previously untreated'**), or had received haemophilia treatments (such as replacement factor eight) on 5 days or fewer (classed as **'minimally treated'**)
- had not previously formed factor eight inhibitors, and did not have factor eight inhibitors at the time they joined the study
- had not previously had intracranial haemorrhage and did not have any signs of an intracranial haemorrhage at the time they joined the study.

Infants could not take part in the study if they:

- had diseases or conditions other than haemophilia A that might have increased their risk of bleeding
- had been treated with emicizumab prophylaxis before.

3. What is happening during this study?

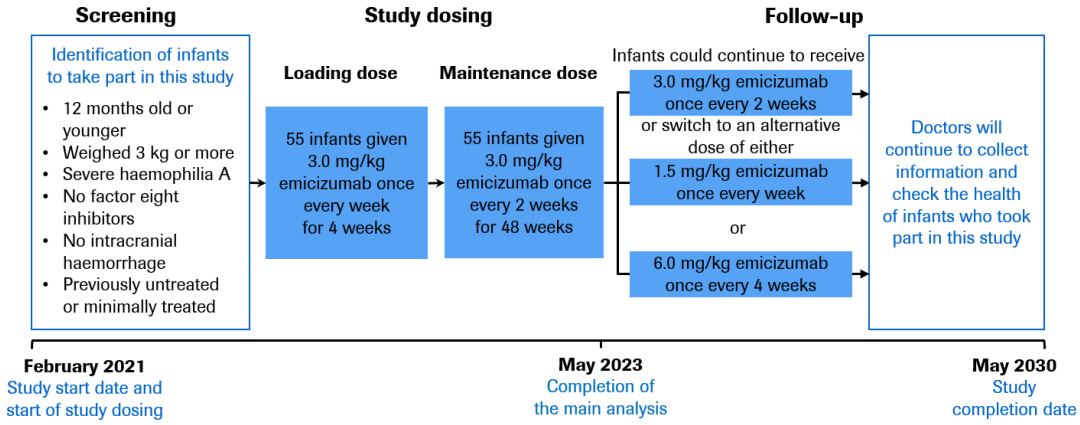
The 55 infants in this study first received 3.0 mg/kg emicizumab once every week for 4 weeks to quickly build up the levels of emicizumab in the body (these doses were known as **'loading doses'**).

After the first 4 weeks, infants received 3.0 mg/kg emicizumab once every 2 weeks for 48 weeks (these doses were known as **'maintenance doses'**).

After 52 weeks, all infants entered a long-term follow-up, where they continued to receive emicizumab at one of the approved doses (1.5 mg/kg of emicizumab every week, 3.0 mg/kg of emicizumab once every 2 weeks, or 6.0 mg/kg of emicizumab once every 4 weeks) based on parent/caregiver choice. Forty-nine infants continued to receive 3.0 mg/kg of emicizumab once every 2 weeks, five infants were switched to 6.0 mg/kg emicizumab every 4 weeks, and one infant had his dose of emicizumab increased from 3.0 mg/kg once every 2 weeks to 3.0 mg/kg once every week, at the request of his study doctor.

The long-term follow-up is planned to last for 7 years, where doctors will continue to monitor infants receiving emicizumab to measure how well the treatment works at preventing bleeds and how safe it is. Doctors will also monitor the health of the joints in infants during the study.

Look below to see more information about what happened in the study.

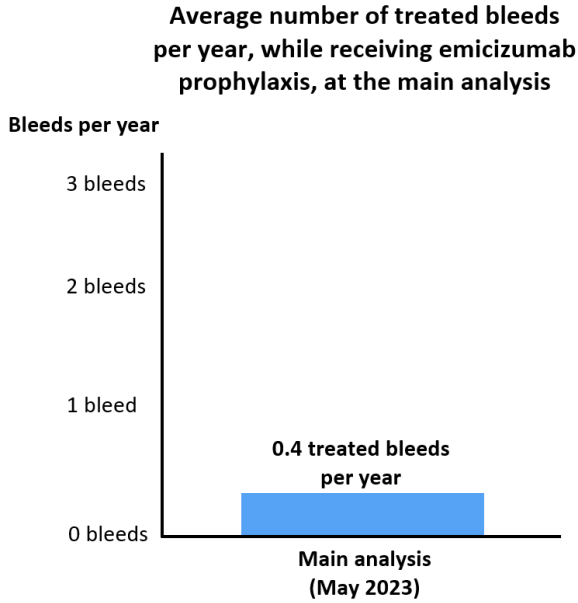


4. How many bleeds did infants on the study experience?

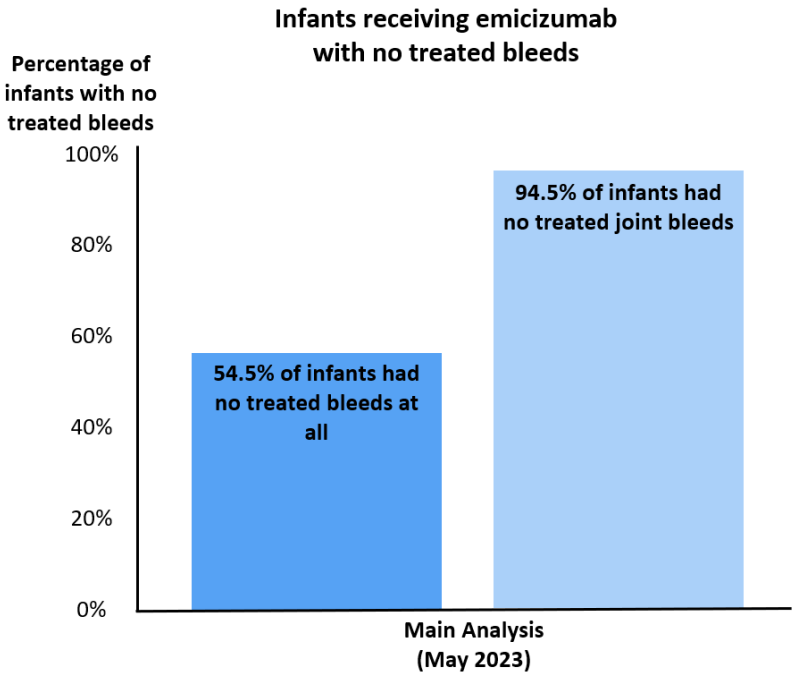
If an infant had a bleed while taking part in the study, the bleed could be treated, if needed, with another type of medication, such as factor eight replacement. Bleeds that are treated in this way are called **'treated bleeds'**.

Study doctors looked at how many treated bleeds occurred over the course of the study, when infants were receiving emicizumab to prevent bleeding. Doctors then used the numbers of treated bleeds to estimate the average number of treated bleeds experienced by an infant over a year.

On average, infants who received preventive emicizumab treatment had less than one treated bleed per year (0.4 bleeds per year reported at the main analysis).



During the study, all treated bleeds were **traumatic bleeds**, meaning that they happened following trauma or injury such as having a fall.



Study doctors also looked at how many infants in the study did not have any treated bleeds while receiving emicizumab. This gives an idea of how well emicizumab works to prevent bleeds that need additional treatment. At the time of the main analysis, 30 out of 55 infants (54.5%) receiving emicizumab had no treated bleeds at all.

Treated bleeds can happen anywhere in the body, including into the joints. Study doctors also looked at how many infants in the study did not have any treated bleeds specifically into their joints while receiving emicizumab. At the time of the main analysis, 52 out of 55 infants (94.5%) had zero treated joint bleeds.

5. What other results were reported in this study?

Question 1: Did any infants taking part in the study experience intracranial haemorrhage while receiving emicizumab?

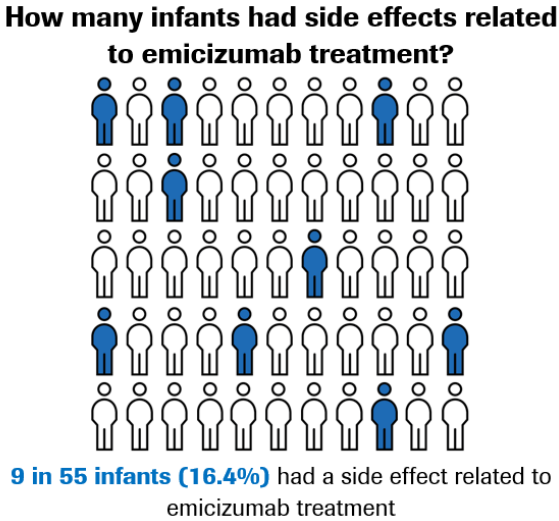
As previously mentioned, infants with haemophilia A who do not receive treatment in their early years of life have an increased risk of bleeding within the head (intracranial haemorrhage). No infants on this study had an intracranial haemorrhage.

Question 2: What side effects did infants taking part in the study have that were related to emicizumab?

Side effects (also known as **'adverse events'**) are unwanted medical problems that happen during the study; they can be related or unrelated to the study treatment. Side effects can vary in severity from **mild** to **serious** and may vary from person to person.

The study doctors believed that the side effects described below were related to emicizumab treatment. 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.

At the time of the main analysis, 9 out of 55 infants (16.4%) had treatment-related side effects. All of these treatment-related side effects were skin reactions where the emicizumab injection was given (such as pain, itchiness, swelling or redness at the site of injection), which is called an '**injection site reaction**'. Injection site reactions were considered to be mild. A side effect is considered 'mild' if it causes slight discomfort, lasts less than 2 days, and no treatment is needed. None of the side effects led to a change in emicizumab treatment.



Serious side effects related to emicizumab

A side effect is considered 'serious' if it is life-threatening, requires hospital care, causes lasting problems and severe limitation of activity, or causes death. No infants in the study had a serious side effect that the study doctors believed could be related to emicizumab.

Other side effects

After receiving factor eight replacement treatment to treat bleeds or prevent the risk of bleeds during surgery, two infants (3.6% of the infants in the study) formed inhibitors against factor eight treatment. Both infants who formed inhibitors continued to receive emicizumab, as emicizumab also works in people with factor eight inhibitors.

6. How does this study help research?

The results presented could help doctors and the community to learn more about the effect of emicizumab in infants with severe haemophilia A.

The results show that infants (children under 12 months old) receiving emicizumab experienced, on average, 0.4 bleeds every year. The results also show that emicizumab did not cause any serious side effects.

No single study can tell us everything about the potential 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 treatment.

7. What are the next steps of the study?

The 7-year long-term follow-up period of the study will provide more information on the management of haemophilia A in children who start emicizumab treatment soon after birth. Over the 7 years, information will continue to be collected on how successful emicizumab is in treating bleeds, and the long-term safety of emicizumab. In addition, information will be collected on the joint health of infants taking part in the study.

8. Where can I find more information?

- You can find more information about this study on the website listed below:
  - https://clinicaltrials.gov/study/NCT04431726.
- If you would like to find out more about the results of this study, the full title of the relevant scientific publication is: "Emicizumab prophylaxis in infants with hemophilia A (HAVEN 7): primary analysis of a phase 3b, open-label trial".
- The authors of the scientific paper are: Steven W. Pipe, Peter Collins, Christophe Dhalluin, Gili Kenet, Christophe Schmitt and others.
- The publication is available in the journal *Blood*, volume number 143, pages 1355–64.

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 your child took part in this study and you have any questions about the results, speak with the study doctor or other staff at the study hospital or clinic. If you have questions about the treatment of your child, speak to the doctor in charge of their 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 Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Emicizumab in Participants from Birth to 12 Months of Age With Hemophilia A Without Inhibitors (HAVEN 7)”.
- The study is known as ‘HAVEN 7’.
- The protocol number for this study is: MO41787.
- The ClinicalTrials.gov identifier for this study is: NCT04431726.
- The EudraCT number for this study is: 2020-001733-12.

9. Infographic summary

A study to look at how effective and safe emicizumab is at preventing bleeding in infants (children under 12 months old) with severe haemophilia A without inhibitors

This is a summary of the results of a study, written for the members of the public and the caregivers of the infants who took part. This study started February 4, 2021, and is expected to end in May 2030. This summary contains results from the main analysis, information was collected up until May 22, 2023 (when infants had been receiving emicizumab for at least 52 weeks).

Why is this study being done?

Haemophilia A, a rare **inherited** bleeding disorder, stops the blood from clotting properly, meaning people with haemophilia A have a lot of bleeds.

Often, treatments to prevent bleeds are not given to infants with haemophilia A until they are older than 1 year, leaving them at risk of life-threatening bleeds within the head, called **intracranial haemorrhages**.

A medicine called emicizumab has been shown to help prevent bleeding in people with haemophilia A of all ages. The method of giving emicizumab is different from other haemophilia A treatments, and allows the treatment to be given from birth.

Doctors are doing this study to look at how well emicizumab prevents bleeds in infants with **severe haemophilia A** without **inhibitors against factor eight**, and whether emicizumab is safe for use in infants.

Who is taking part in this study?

This study is taking place at:

32 centres across the world

14 countries around the world

55 male infants with severe haemophilia A without factor eight inhibitors took part

25 infants were younger than **3 months old**

30 infants were between **3 and 12 months old**

What is happening during this study?

Loading dose (emicizumab 3 mg/kg once a week) for the first four weeks.

Maintenance dose (emicizumab 3 mg/kg once every 2 weeks) for at least 48 weeks.

Infants entered a **7-year follow-up**, receiving emicizumab at one of the approved doses based on parent/caregiver choice.

- Emicizumab 1.5 mg/kg **once every week**

OR

- Emicizumab 3 mg/kg **once every 2 weeks**

OR

- Emicizumab 6 mg/kg **once every 4 weeks**

How many bleeds did infants on the study experience?

On average, infants who received emicizumab had **fewer than one treated bleed per year.**

0.4 bleeds per year were reported.

All treated bleeds were **traumatic bleeds**, meaning they occurred following trauma or injury, such as having a fall.

More than half of the infants had **no treated bleeds** at all.

of infants had **no treated bleeds**

of infants had **no treated joint bleeds**

What other results were reported in this study?

No infants had an **intracranial haemorrhage.**

Nine out of **55** infants (16.4%) had side effects related to emicizumab.

All treatment-related side effects were skin reactions where the emicizumab injection was given. Examples include **pain, itchiness, swelling** or **redness** at the site of injection.

No infants had a **serious side effect** that study doctors believed could be related to emicizumab.

Two infants (3.6% of the infants in the study) formed **inhibitors against factor eight**.

What does this study tell us?

The results show that infants (children under 12 months old) who received emicizumab had, on average, 0.4 treated bleeds every year. The results also show that emicizumab did not cause any serious side effects.

This study is known as 'HAVEN 7' (NCT04431726) and was organised and paid for by F. Hoffmann-La Roche Ltd.
¦ M-XX-00017293 ¦ Date of preparation: May 2024.

For the definition of **'inherited'**, **'severe haemophilia A'**, **'inhibitors against factor eight'**, **'loading dose'**, **'maintenance dose'**, **'traumatic bleeds'**, **'intracranial haemorrhage'**, and **'serious side effects'**, please see the glossary section of the layperson summary.

10. Glossary

Adverse events	An unwanted medical problem that happens when taking a medicine. It may or may not be related to the medicine.
Central venous access device	A device that is inserted into the body through a vein to allow for fluids, blood products, medication, and other therapies to be injected directly into the bloodstream. The device can make it easier to access veins when frequent and long-term injection into veins is needed. It can often stay inserted into the body for a year or longer.
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.
Gene	Genes are units of DNA inherited from our parents that contain all the information needed to make people who they are – from the colour of someone's eyes to their blood type. DNA is the code that carries the instructions to build all known living organisms, from bacteria to humans.
Inherited	Passed on from one generation to the next through certain genes.
Inhibitors against factor eight	Antibodies produced as a reaction by the body's immune system in response to treatment with replacement factor eight. Inhibitors against factor eight can stop replacement factor eight treatment from working to prevent or stop 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.
Intracranial haemorrhage	Bleeding within the skull, which can be life threatening.
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 two days, and does not need any treatment.

Minimally treated	Participants who have had up to five days of exposure with haemophilia-related treatments such as replacement factor eight.
Factor eight mimicking antibody	A treatment for haemophilia that works in a different way than directly replacing the missing clotting factor; instead, this treatment mimics how clotting factor eight works.
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 that was started after the drug company has asked for approval from health authorities for doctors to give the drug to patients, but before this approval was given. The study can be used to gather more information about a drug in specific groups of people.
Previously untreated	Participants who have not received any haemophilia treatment prior to the study
Prophylactic treatment	Treatment given on a regular basis. In people with haemophilia A, this is given to prevent bleeding and later joint and muscle damage, which can be caused by bleeding.
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 A. This can be taken from human blood donations, or artificially created in a laboratory. There are two types of factor eight treatment – standard half-life and extended half-life – which refers to how long factor eight in the body stays at an effective level after treatment is given. Extended half-life factor eight treatment stays in the body for longer after treatment than standard half-life factor eight treatment.
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.
Severe haemophilia A	People with severe haemophilia A have factor eight activity of less than 1% of the level observed in someone without haemophilia.

Side effect	An unwanted medical effect that happens when taking a medicine and is believed by clinicians to be related to the medicine.
Subcutaneous injection	An injection under the skin between the skin and muscle.
Thrombosis	A blood clot that forms inside a blood vessel, which can cause it to become blocked.
Traumatic bleeds	Bleeds were classified as traumatic if parents/caregivers recorded a bleed following trauma or an injury such as having a fall. Bleeds that occurred because of a procedure or surgery were not counted as a 'traumatic bleed'.
Treated bleed	A bleed treated with replacement factor eight or other treatment.
X chromosome	One of two sex-determining chromosomes in humans, of which males have one, and females have two.