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BIOMARIN

The full title of this study is:
Two-year outcomes of valoctocogene roxaparvovec therapy for hemophilia A

Plain Language Summary

Outcomes for men with severe hemophilia A 2 years after treatment with valoctocogene roxaparvovec gene therapy

This infographic was developed and funded by Biomarin.
This material is intended for healthcare professionals only.
Roctavian (valoctocogene roxaparvovec) prescribing information can be found here.

This summary contains information on an article published in *The New England Journal of Medicine*.

View article

Date of summary: June 2023

More information can be found at:
- clinicaltrials.gov/ct2/show/NCT03370913
- https://www.youtube.com/watch?v=NIH0slUPg9A

How to say…

Gene therapy: jeen THER-uh-pee
Hemophilia: hee-muh-FIL-ee-uh
Prophylaxis: pro-fil-AC-sis
Valoctocogene roxaparvovec: val-octo-CO-jeen roxa-PARVO-vek

What is the background to this study?

What is hemophilia A?

- Hemophilia A is a mostly inherited condition that causes affected people to **bleed too easily**
  - ~ An inherited condition is a condition that can be passed down from parent to child
- People with hemophilia A have **missing or low levels** of a blood clotting factor known as **factor VIII (8)**. Factor VIII is a protein that **helps the blood to clot**
  - ~ This means it helps the blood turn from a liquid state to a gel-like state to stop bleeding, for example when you cut yourself
  - ~ People with hemophilia A have a change (called a "mutation") in their DNA, specifically the **F8 gene**. DNA is the body's "instruction book" and "genes" are specific segments of your DNA
  - ~ The F8 gene contains the specific instructions to **make factor VIII**. This change in the F8 gene means that people with hemophilia A cannot make the right amount of working factor VIII
- Without factor VIII it is **more difficult to stop bleeding**. This can affect things like a simple cut but also means that people with hemophilia A bruise easily and can bleed inside the body
- The amount of factor VIII in the blood determines the severity of hemophilia. The lower the amount of factor VIII, the more likely it is that bleeding will occur
- Standard treatment for hemophilia A currently involves replacing missing factor VIII with artificial factor VIII or using treatments that do the same job. These treatments are given by infusion into the blood and might be needed up to several times a week

Definitions…

Normal factor VIII levels are **40 IU/dL* and above**

Mild hemophilia A factor VIII levels are **above 5 to less than 40 IU/dL**

Moderate hemophilia A factor VIII levels are **1 to 5 IU/dL**

Severe hemophilia A factor VIII levels are **less than 1 IU/dL**

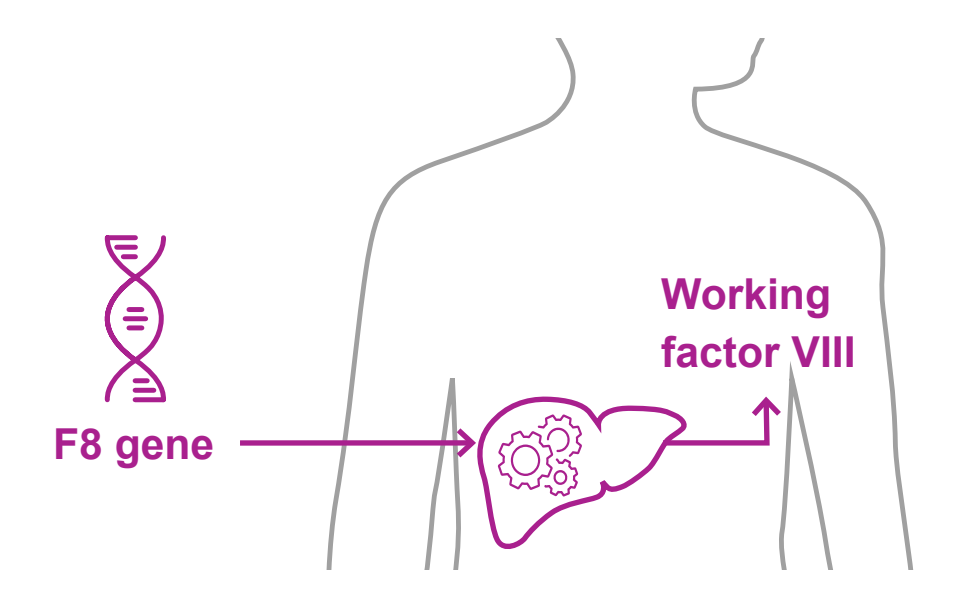
*IU/dL means international units per deciliter. This is the standard unit for measuring factor VIII levels and reflects the percentage of normal factor VIII levels (1 IU/dL = 1%).

What is gene therapy?

Gene therapy is a treatment that delivers instructions, coded by genes, to the patient. This enables them to make working versions of the right proteins.

Working gene → A "vector" is the vehicle (substance) that carries the working gene through/in the body → Working gene given by infusion into the blood → Person now has the working gene with instructions to make the proteins that work properly

- **Valoctocogene roxaparvovec** is a gene therapy treatment for people with **severe hemophilia A**
- **Valoctocogene roxaparvovec** works by transferring **working copies** of the **F8 gene** into liver cells. The F8 gene gives instructions to the liver cells to make working factor VIII proteins



What is this study looking at?

What is the aim of this study?

- This study, known as GENEr8-1, looks at how well valoctocogene roxaparvovec works for treating people with severe hemophilia A compared with standard treatment with factor VIII replacement
- Researchers want to know if this gene therapy will have long-lasting benefits on factor VIII levels and how well it controls bleeding in people with hemophilia A

Why is this study important?

- Gene therapy aims to give people with hemophilia A the ability to **make their own working factor VIII**. This means they might not have to rely on replacing factor VIII with regular injections (known as "prophylaxis"), which is the current standard treatment
  - ~ "Prophylaxis" means using a treatment to try to prevent disease. In hemophilia A, this means giving factor VIII infusions in advance to try to help the blood clot in order to stop bleeding

Who is taking part in this study?

Adult men (aged over 18):

- With severe hemophilia A
- Who had been receiving regular factor VIII infusions for at least 1 year before the study started
- Living in one of the countries included in this international study: Australia, Belgium, Brazil, France, Germany, Israel, Italy, Republic of Korea, South Africa, Spain, Taiwan, the UK, and the US

NOT included:

- Men with certain proteins in their blood that could affect how well the treatment would work, such as:
  - ~ Proteins the body produces against factor VIII (sometimes referred to as "inhibitors")
  - ~ Proteins against the vector that carries the gene in/through the body
- Men with liver problems
- Men with HIV (researchers excluded men with HIV after the start of the study)

112 men from another study of factor VIII infusions in hemophilia A
22 men enrolled directly into GENEr8-1

→ **134 men** received a **single dose** of **valoctocogene roxaparvovec** → Year 1 → Year 2 → **132 men** are still in the study 2 years after gene therapy was given

What are the researchers measuring?

How WELL the gene therapy works

Any bleeding episode	Any time they have a factor VIII infusion	Factor VIII levels
[reported by patients]		[measured by researchers]

How SAFE the gene therapy is

Any side effects	Blood test values
[reported by patients]	[measured by researchers]

What are the results of the study so far?

By the end of 2 years of treatment, men who received a single dose of valoctocogene roxaparvovec were **producing their own factor VIII** and **no longer depended on regular injections** to protect themselves from bleeds.

7 in 10 men had no bleeding episodes needing treatment

Only 6 out of 132 men still in the study returned to regular factor VIII infusions ("prophylaxis") so far

5 of these men had factor VIII levels of less than 5 IU/dL, in the moderate or severe hemophilia A range.

Did valoctocogene roxaparvovec reduce the number of factor VIII infusions needed?

On average, 2 years after gene therapy, **98%** **less factor VIII was infused** per year compared with before treatment

For an average 80kg man, this means:

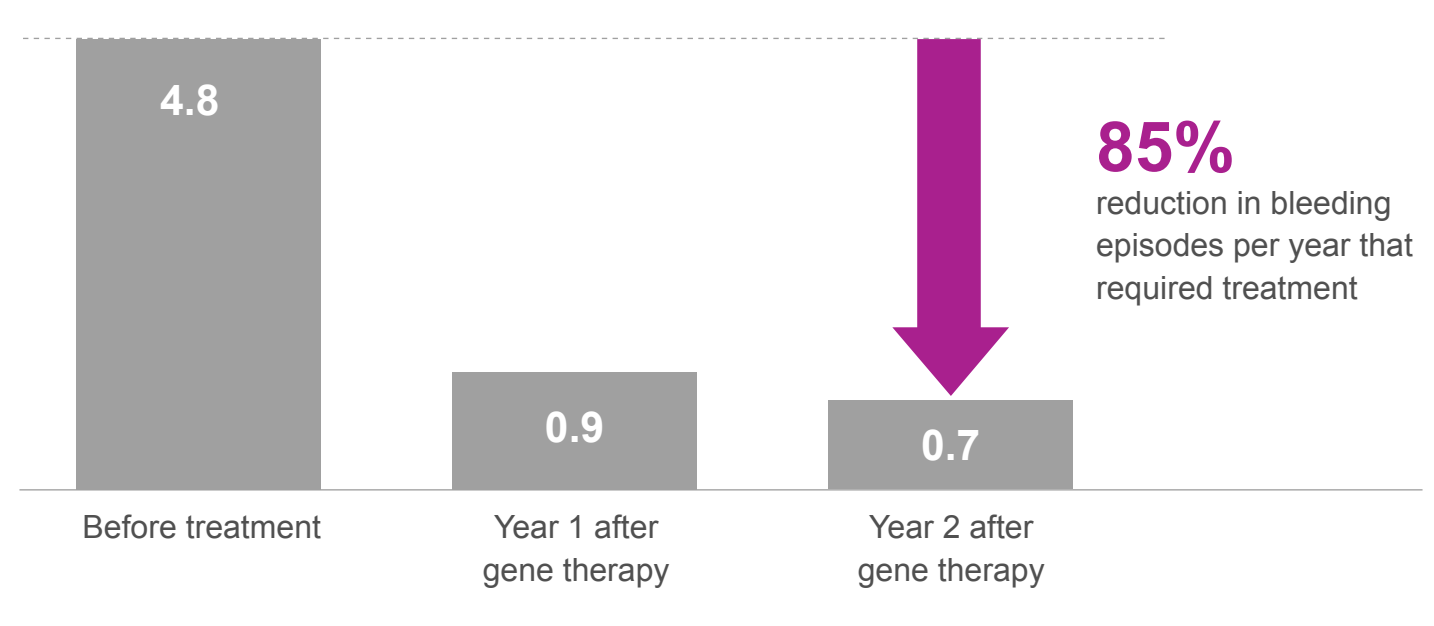
Nearly **320,000** units of factor VIII were infused per year **before treatment**

Less than **7,200** units of factor VIII were infused per year **2 years after treatment**

Did valoctocogene roxaparvovec increase the patient's own factor VIII levels?

77% of men had factor VIII levels in the **normal or mild hemophilia range** after 2 years

The average number of bleeds per year that needed treatment decreased from almost **5** before gene therapy to **less than 1** after treatment.



What were the side effects?

Most side effects happened in the first year after treatment and were mild.

- The most common side effect was an **increase in liver enzyme levels**. An enzyme is a protein that speeds up chemical reactions and is needed for many processes in the body

- In most cases, the increase in liver enzymes **did not cause symptoms**
- Liver enzymes increased because of an **immune response** to the medication. An "immune response" is the way the body defends itself against substances that it sees as harmful or foreign
- This was treated with medication, mainly **steroids**, to calm the immune response

8 in 10 men needed steroids for liver enzyme increase at some point after receiving gene therapy, for an average of 35 weeks

- **Only 1 in 132 men still needed steroids at the end of Year 2**

Other side effects included: Headache, Nausea, Joint pain

These occurred in more than 30% of men, and none of these were serious

What are the conclusions of the study?

Compared with standard treatment, 2 years after receiving gene therapy, men with hemophilia A:

had **fewer bleeding episodes**
- There was an **85%** decrease in yearly bleeding rate

needed **fewer factor VIII infusions** to treat bleeds
- There was a **98%** decrease in yearly factor VIII use

had **higher average** factor VIII levels
- **77%** of men had factor VIII levels in the normal or mild hemophilia range

The **side effects were mild**, and there were no concerns about any unwanted effects the treatment might have.

Are there any plans for further studies?

Researchers will continue to look at the participants in this study to understand the long-term safety and treatment effects of gene therapy with valoctocogene roxaparvovec. They plan to follow participants for up to 15 years to see these effects.

Supporting information

Who sponsors this study?

This study is sponsored by BioMarin Pharmaceutical Inc.

BioMarin Pharmaceutical Inc., Novato, CA.

The sponsors would like to thank everyone who took part in this study.

Where can I find more information?

For more information on this study, please visit:
clinicaltrials.gov/ct2/show/NCT03370913

View article

This is a plain language summary (PLS).
The purpose of this summary is to help you understand the results of research, originally published in a peer-reviewed scientific journal, where articles are reviewed by other researchers before publication.

- Valoctocogene roxaparvovec can be prescribed in the EU to treat people with severe hemophilia A. At the date of this PLS, valoctocogene roxaparvovec is also being considered for approval by the U.S. Food and Drug Administration
- Researchers must look at the results of many types of studies to understand whether a study drug works, how it works, and whether it is safe to prescribe to patients
- This summary reports the results of only 1 study. The results of this study may be different from the results of other studies that researchers look at
- This PLS is not peer-reviewed. The publisher of the original manuscript was not involved in the preparation of the PLS and has not reviewed this content

Who wrote this summary?

Gillian Lowe[1]; Simon Fletcher[2]; Patrick James Lynch[3]; Johnny Mahlangu[4]; Margareth C Ozelo[5]; Luke Pembroke[6]; Steven W Pipe[7]; Gabriela G Yamaguti-Hayakawa[5]; Deon York[8]; Tara M. Robinson[9]; Hua Yu[9]; Leonard A. Valentino[10]

Affiliations

[1]West Midlands Adult Comprehensive Care Haemophilia Centre, University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW

[2]Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, OX3 7LE, UK

[3]Believe Limited, Los Angeles, CA, USA

[4]Hemophilia Comprehensive Care Center, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand and NHLS, Johannesburg, South Africa

[5]Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, SP, Brazil

[6]Haemnet, London, UK

[7]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA

[8]Haemophilia Foundation of New Zealand, Christchurch, New Zealand

[9]BioMarin Pharmaceutical Inc., Novato, CA, USA

[10]National Hemophilia Foundation, New York, NY, USA; Internal Medicine and Pediatrics, Rush University, Chicago, IL, USA

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