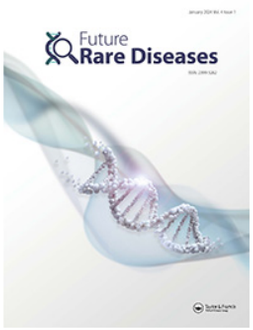

Future Rare Diseases

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Plain language summary of 4-year results of the GENEr8-1 clinical trial of valoctocogene roxaparvovec gene therapy for hemophilia A

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Where can I find the original article on which this summary is based?

The original article, 'Efficacy, safety, and quality of life 4 years after valoctocogene roxaparvovec gene transfer for severe hemophilia A in the phase 3 GENEr8-1 trial,' is free to access at: https://www.sciencedirect.com/science/article/pii/S2475037924003108.

Summary

What is this summary about?
Factor VIII ('FVIII') is a protein important for blood clotting. Hemophilia A occurs when *F8* – the **gene** that is required to produce FVIII – is not functional, leading to excessive bleeding. Typically, people with hemophilia A use FVIII concentrate or **emicizumab** to prevent bleeding. Valoctocogene roxaparvovec (ROCTAVIAN) is the first approved gene therapy for hemophilia A that delivers functional copies of *F8* to the liver to enable the body to produce its own FVIII and prevent excessive bleeding.

What was the objective of this study?
To determine whether valoctocogene roxaparvovec continues to provide people with severe hemophilia A better protection against bleeding than FVIII concentrate 4 years after treatment.

How to say (download PDF and double click sound icon to play sound)…

- **Valoctocogene roxaparvovec:** Val-octo-CO-jeen roxa-PARVO-vek
- **Prophylaxis:** Pro-fi-lax-is
- **Hemophilia:** Hee-muh-FIL-ee-uh
- **Adeno-associated virus (AAV):** ADD-en-o associated virus (A-A-V)
- **Alanine aminotransferase (ALT):** Al-ah-neen ah-mean-oh-trans-fear-aze (A-L-T)
- **Emicizumab:** Eh-mih-SIZ-oo-mab

Gene: A template made of DNA that the body uses to produce proteins.

Emicizumab: An antibody that is designed to mimic the ability of FVIII to clot blood; emicizumab is an approved therapy for hemophilia A that is used for prophylaxis against bleeding.

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What were the results?

A total of 134 men with severe hemophilia A enrolled in the GENEr8-1 study and received a single infusion of valoctocogene roxaparvovec. After ending regular FVIII **prophylaxis**, the average number of bleeds that required treatment dropped 83%, from ~5 bleeds per year to ~1 bleed per year. Furthermore, 74% of **participants** had no bleeds requiring treatment during year 4. The average FVIII level was 16% at the end of year 4. Overall, 110 of 134 participants remain off prophylaxis. Elevated levels of the liver enzyme **alanine aminotransferase** (a sign of liver inflammation) occurred in 43% of participants in year 4; however, no participants required steroids to treat the elevations during year 4.

Prophylaxis: A treatment aimed at preventing an event from occurring.

Participant: A person who meets the criteria to be included in a study and chooses to take part.

Alanine aminotransferase (ALT): An enzyme (a type of protein) that is commonly monitored by doctors as a sign of liver inflammation.

What do the results mean?

A single infusion of valoctocogene roxaparvovec continued to provide better protection against bleeds on average than prophylaxis with regular infusions of FVIII concentrate, and most participants remained off prophylaxis and had mild or non-hemophilia FVIII levels. The risk-benefit balance for valoctocogene roxaparvovec did not change and remains favorable.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you understand the findings from recent research. Valoctocogene roxaparvovec is approved to treat the condition (hemophilia A) that is discussed in this summary. The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence, not on the results of a single study.

Who is this article for?

This article is for people with hemophilia A and their families, friends, caregivers, and health care providers who would like to learn about recent hemophilia A gene therapy research findings. This article may also be used by experts to assist in education about gene therapy.

Who sponsored this study?

The study and this summary were **sponsored** by BioMarin Pharmaceutical Inc.

Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information from the study.

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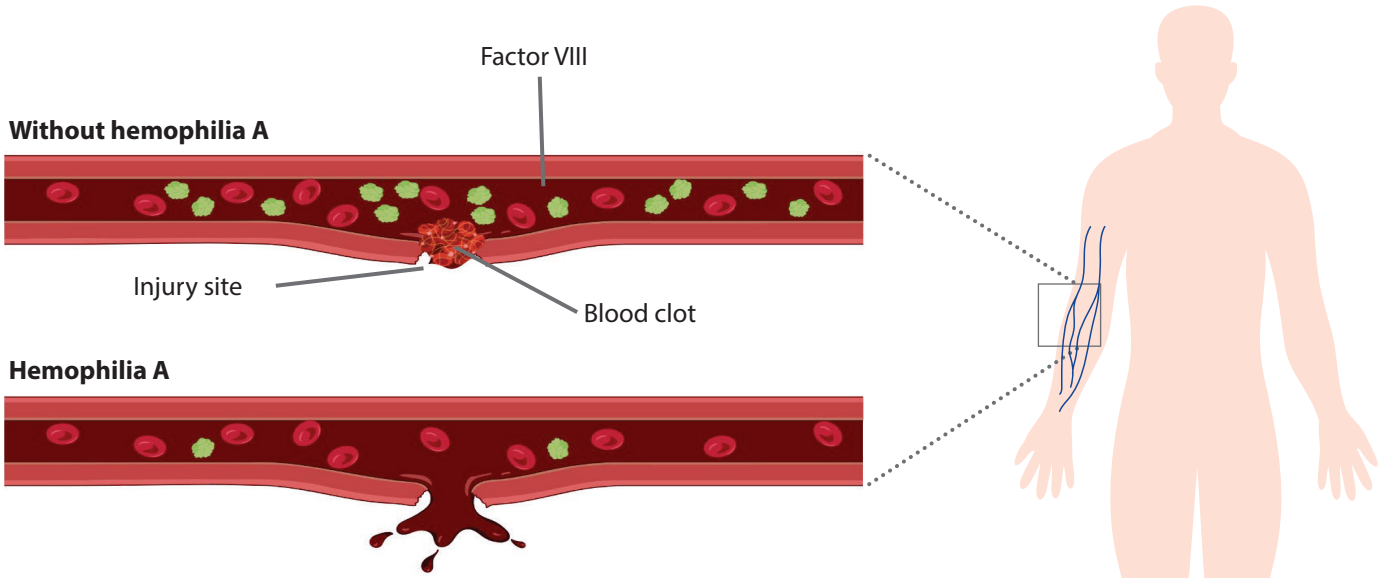
Hemophilia A

Hemophilia A is a bleeding disorder that occurs when the *F8* gene contains faulty instructions for making the protein factor VIII ('FVIII' or 'factor eight'). FVIII is critical for the formation of blood clots when bleeding occurs. Health-related quality of life – how a person's general well-being and functioning is affected by their health – is impacted by hemophilia A, including negative effects on mental health, relationships, and employment.

Hemophilia A is an inherited disorder that causes people to bleed easily because they have lower-than-normal levels of **FVIII**, a blood-clotting protein



Factor VIII

In **mild hemophilia A**, when FVIII levels are between 5% and 40%, major injuries and surgeries can cause excessive bleeding, but spontaneous bleeds rarely occur

In **moderate hemophilia A**, when FVIII levels are between 1% and 5%, excess bleeding occurs with minor injuries, and spontaneous bleeds occur occasionally

In **severe hemophilia A**, when FVIII levels are less than 1%, bleeding occurs even with no apparent injury, often into joints and muscles

This figure was created using assets from BioRender. Ghane, A. (2025) https://BioRender.com/mwtyxg1

Preventing bleeds in people with hemophilia A

The goal of prophylaxis in hemophilia A is to prevent episodes of abnormal or excessive bleeding. This is typically achieved by replacing missing FVIII in the body with commercially produced FVIII concentrate.

The drug emicizumab can also be used for prophylaxis. Both drugs reduce the frequency of bleeds, but they must be injected regularly to be effective.

The need for lifelong regular prophylactic treatments creates burdens for patients that can negatively affect their health-related quality of life. Even with prophylaxis, bleeding episodes still occur either spontaneously or because of injury. When this happens, FVIII concentrate must be infused promptly to stop the bleed.

Valoctocogene roxaparvovec

The first approved gene therapy for hemophilia A

Valoctocogene roxaparvovec (ROCTAVIAN) is a gene therapy for severe hemophilia A. Gene therapy works differently than FVIII concentrate or emicizumab to prevent bleeding: instead of replacing or mimicking the activity of FVIII, it addresses the lack of genetic instructions for making FVIII. Valoctocogene roxaparvovec consists of a set of genetic instructions for FVIII delivered to the cells within the body inside of a **vector**, the empty 'shell' of the **adeno-associated virus ('AAV')** that cannot replicate itself like a normal virus does.

How does it prevent bleeding?

Valoctocogene roxaparvovec is designed to allow people with hemophilia to make their own FVIII. There are 3 main parts of valoctocogene roxaparvovec:

- The **vector genome** contains instructions the body uses to make FVIII. The instructions are similar to the natural version of *F8*, but slightly shortened to allow them to fit inside the vector
- The **promoter** specifies which type of cell can read the FVIII instructions. In the case of valoctocogene roxaparvovec, the instructions are for liver cells to read
- The vector, which is the container the instructions are delivered in

This is the process for the one-time administration of valoctocogene roxaparvovec and FVIII production:

1. Valoctocogene roxaparvovec is delivered into the patient's body through an intravenous infusion
2. When the vector containing the FVIII instructions reaches the intended cells in the liver, the instructions are read by the body and FVIII is produced. While the vector reaches other types of cells, cells outside of the liver are not thought to produce FVIII because they are not able to read the instructions
3. Newly produced FVIII enters the bloodstream, where it helps blood clotting

Vector: A means to deliver a vector genome to the desired cells within the body. In the case of valoctocogene roxaparvovec, the vector is the capsid ('shell') of the AAV.

Adeno-associated virus (AAV): A virus that does not cause disease in humans. For valoctocogene roxaparvovec, the virus has been engineered to remove its ability to replicate and repurposed to carry genetic instructions for FVIII.

Vector genome: The genetic material that the gene therapy delivers to the body to produce the desired benefit. Vector genomes are the units in which a gene therapy dose is measured.

Promoter: A part of the vector genome that directs certain types of cells to read the instructions. In the case of valoctocogene roxaparvovec, the promoter is designed to allow only liver cells to produce FVIII based on the instructions.

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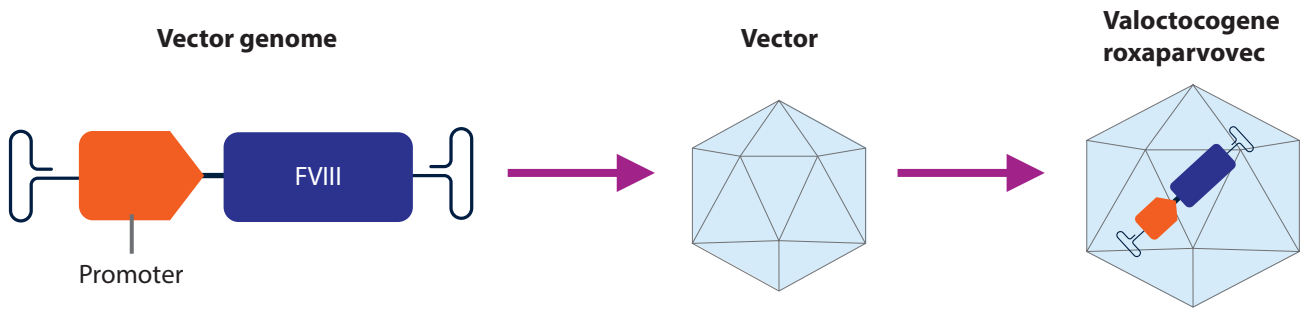
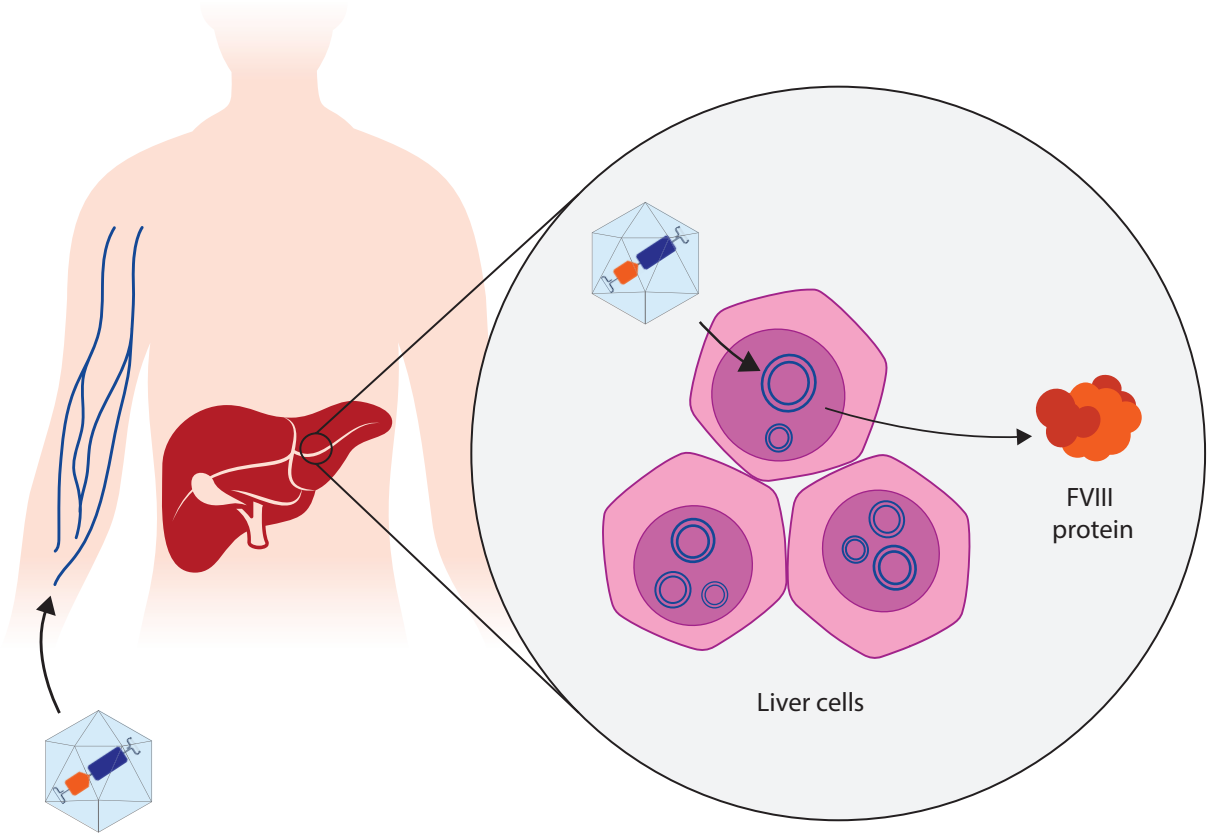


1. The vector genome is packaged into the vector to create valoctocogene roxaparvovec



2. Valoctocogene roxaparvovec is infused

3. FVIII is produced in the liver and circulates throughout the body

GENEr8-1

What is the purpose of the study?
GENEr8-1 is a **phase 3 clinical trial** of valoctocogene roxaparvovec. As a phase 3 trial, GENEr8-1 is meant to determine

- If valoctocogene roxaparvovec works better than a currently approved treatment (prophylaxis with regular FVIII concentrate infusions) in a large group of people
- If the benefits of the treatment outweigh the risks

What is the study testing?
GENEr8-1 measured the following outcomes:

Efficacy
Efficacy is the ability of a drug to produce the intended outcomes. In GENEr8-1, these were

- Bleeding:
  - The number of bleeds that participants experienced per year. These were measured as the number of treated bleeds (bleeds that required FVIII treatment) or any bleeds (regardless of whether treatment was required)
  - Participants with 0 treated bleeds
  - The number of bleeds after valoctocogene roxaparvovec treatment was compared with the number of bleeds when participants were using FVIII in a previous observational study
- Rate of FVIII infusions: the number of FVIII concentrate infusions that participants received per year. This is another way to tell how well participants are protected against bleeding
- FVIII levels: the amount of FVIII produced by the body as a result of gene therapy
- The Haemophilia-Specific Quality of Life Questionnaire for Adults (Haemo-QOL-A): a questionnaire that measures health-related quality of life specifically for people with hemophilia

Safety
Safety was determined by reporting the number of the following events:

- **Adverse events**, which are health-related events that occurred after receiving valoctocogene roxaparvovec. Adverse events are not necessarily related to the treatment and may be purely coincidental
- Alanine aminotransferase ('ALT') elevations, which are a sign of liver inflammation, are a type of adverse event. Since valoctocogene roxaparvovec directs FVIII production to the liver, ALT elevations were monitored closely
- Immunosuppressant use to reduce ALT elevations. Because immunosuppressants can cause their own side effects, lower usage is generally considered better

What happened in the study

1. Adult men with severe hemophilia A who were previously using FVIII prophylaxis and met the other eligibility criteria were enrolled
2. Each participant received a single infusion of valoctocogene roxaparvovec at a dose of $6x10^{13}$ (60 trillion) vector genomes per kilogram of body weight
3. Regular prophylactic FVIII concentrate infusions continued for the first 4 weeks after treatment; after that, FVIII concentrate was used only as necessary for bleeding

Phase 3 clinical trial: After finding the most effective safe dose in phase 1 and 2 trials, phase 3 trials use a larger group of people to determine whether the benefits of the treatment outweigh the risks and whether the treatment works better than a currently approved treatment.

Efficacy: In clinical trials, efficacy is the ability of a treatment to produce the desired effect.

Adverse event: Health-related events that occur after a participant receives a treatment. Not all adverse events are related to the study treatment and may be incidental.

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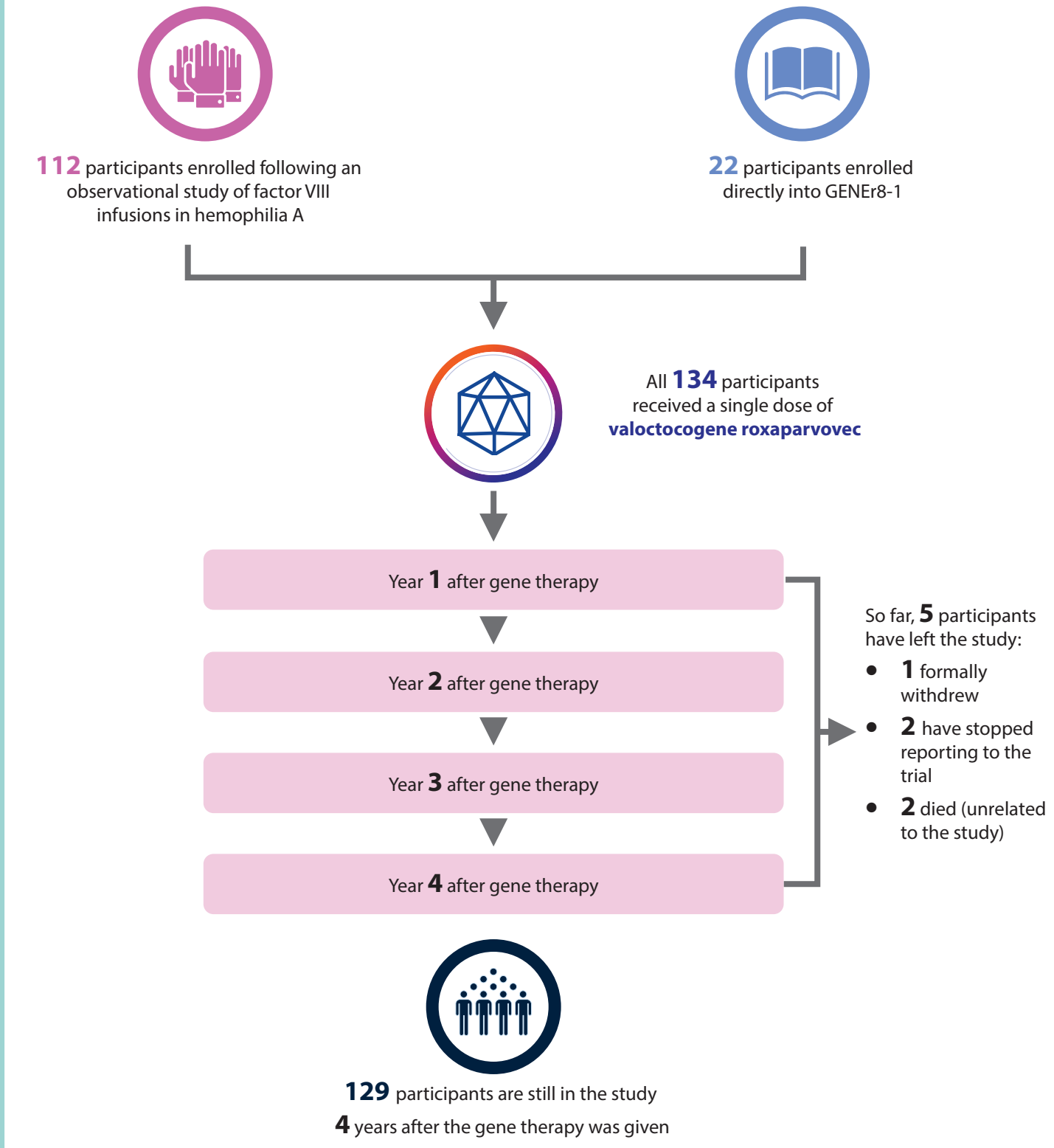
112 participants enrolled following an observational study of factor VIII infusions in hemophilia A
22 participants enrolled directly into GENEr8-1
All 134 participants received a single dose of valoctocogene roxaparvovec
Year 1 after gene therapy
Year 2 after gene therapy
Year 3 after gene therapy
Year 4 after gene therapy
So far, 5 participants have left the study:
1 formally withdrew
2 have stopped reporting to the trial
2 died (unrelated to the study)
129 participants are still in the study
4 years after the gene therapy was given

All participants were:

- Male with severe hemophilia A
- Age 18 years or older
- Previously treated with FVIII for at least 1 year before joining
- Previously treated with FVIII on at least 150 separate days

Patients could not join the study if they had:

- Weakened immune systems
- Substantial problems with liver structure or function
- Liver or kidney problems
- A pre-existing immune response to the vector
- FVIII inhibitors

Goals of the study:

To see how well valoctocogene roxaparvovec prevents bleeding:

- How many bleeds participants experienced per year that needed to be treated with FVIII
- How much manufactured FVIII participants had to use
- How much FVIII the participants made

To determine how safe valoctocogene roxaparvovec is:

- How many adverse events occurred
- How many ALT elevations occurred, a type of adverse event that suggests liver inflammation
- Whether immunosuppressants were used to reduce ALT elevations

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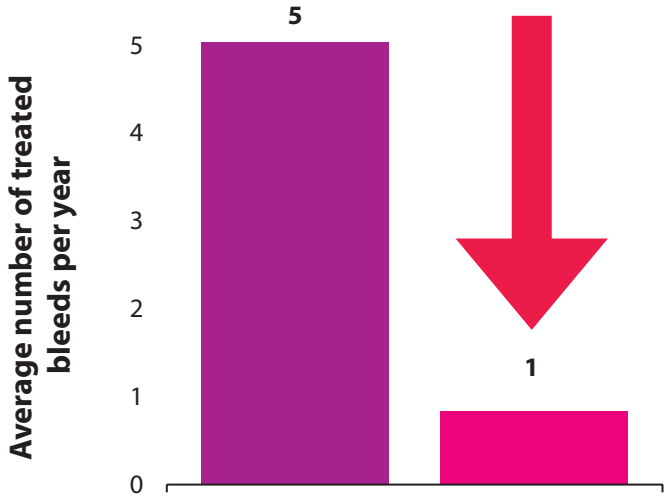
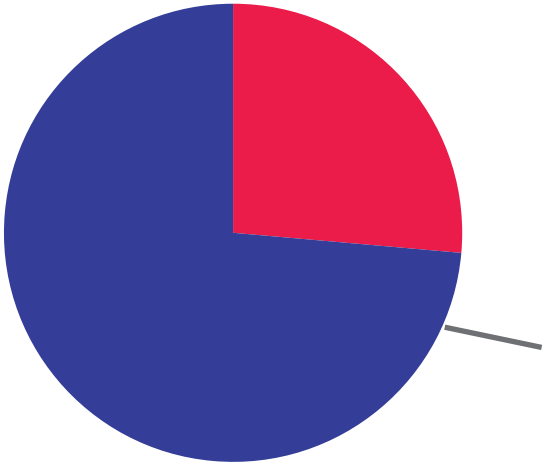
Efficacy results

Bleeding episodes

- Participants experienced an average of 83% fewer bleeds per year that required FVIII treatment after receiving valoctocogene roxaparvovec than when using FVIII prophylaxis before gene therapy.
- On average, participants experienced ~1 treated bleed per year during the first, second, third, and fourth years after receiving valoctocogene roxaparvovec compared with ~5 bleeds per year when using FVIII prophylaxis before gene therapy.
- When using FVIII prophylaxis in the 6 months before receiving gene therapy, 32% of participants had no treated bleeds. In the fourth year after receiving valoctocogene roxaparvovec, 74% of participants had no treated bleeds.
- Nearly 62% of participants had no bleeds at all (treated or untreated) during year 4, up from 30% before gene therapy.



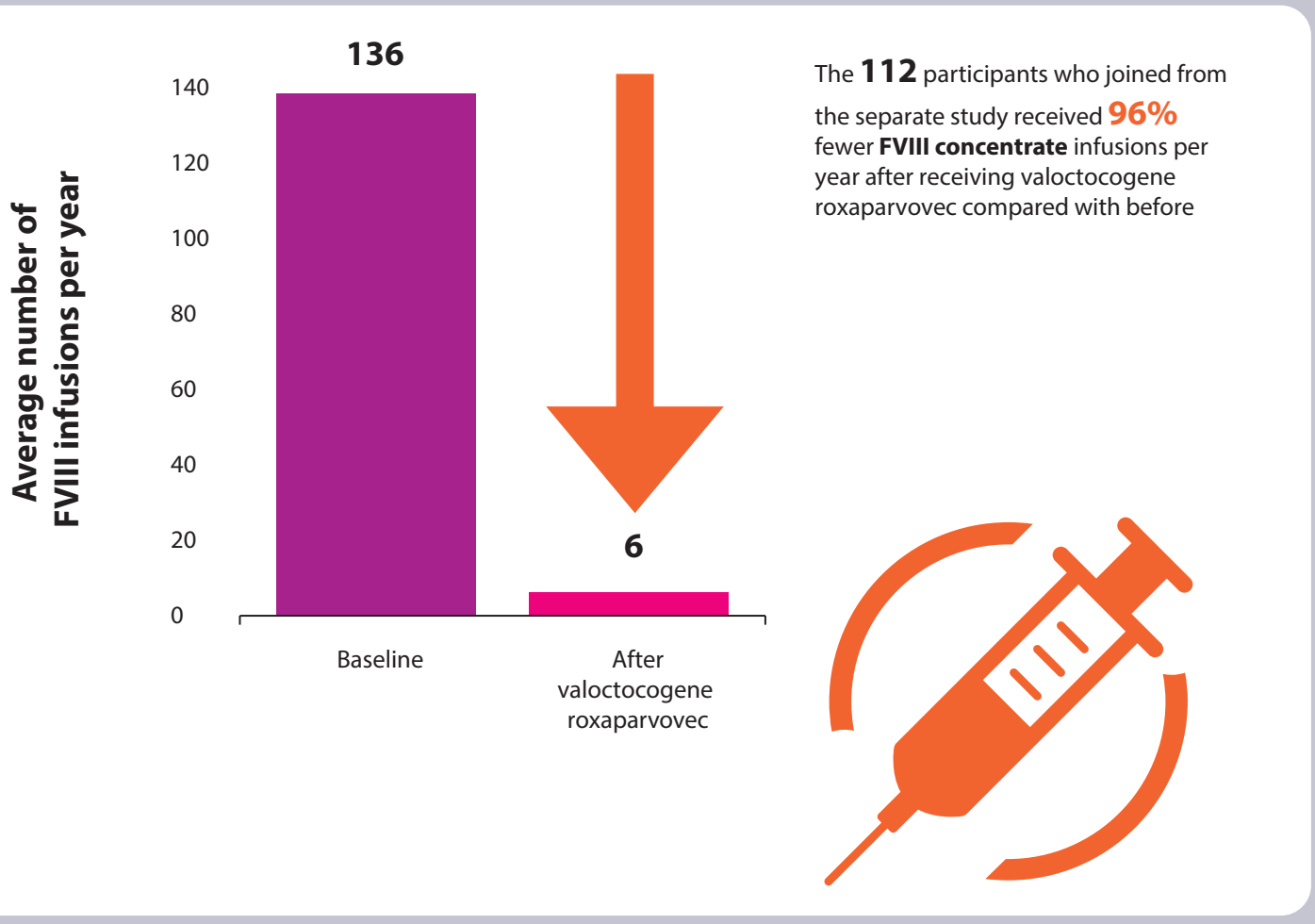
The **112** participants who joined from the observational study had **83%** fewer **bleeds per year** that needed treatment after receiving valoctocogene roxaparvovec compared with before



74% of participants had no **treated bleeds** during Year 4

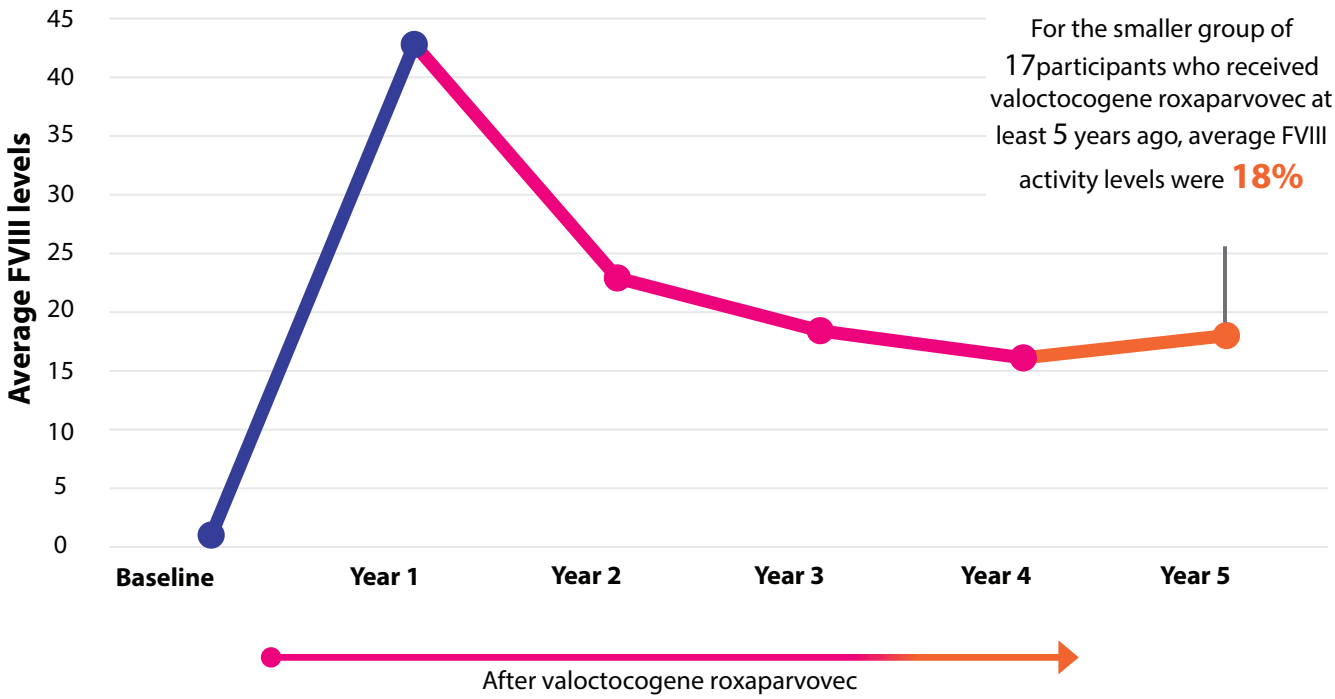
FVIII infusion rate

- Participants used 96% fewer FVIII concentrate infusions after receiving valoctocogene roxaparvovec than when using FVIII prophylaxis before gene therap.y
- On average, participants received 1, 3, 9, and 11 FVIII infusions per year during the first, second, third, and fourth years after receiving valoctocogene roxaparvovec, respectively, compared with 136 infusions per year before gene therapy. These included FVIII infusions used for any reason, including prophylaxis.



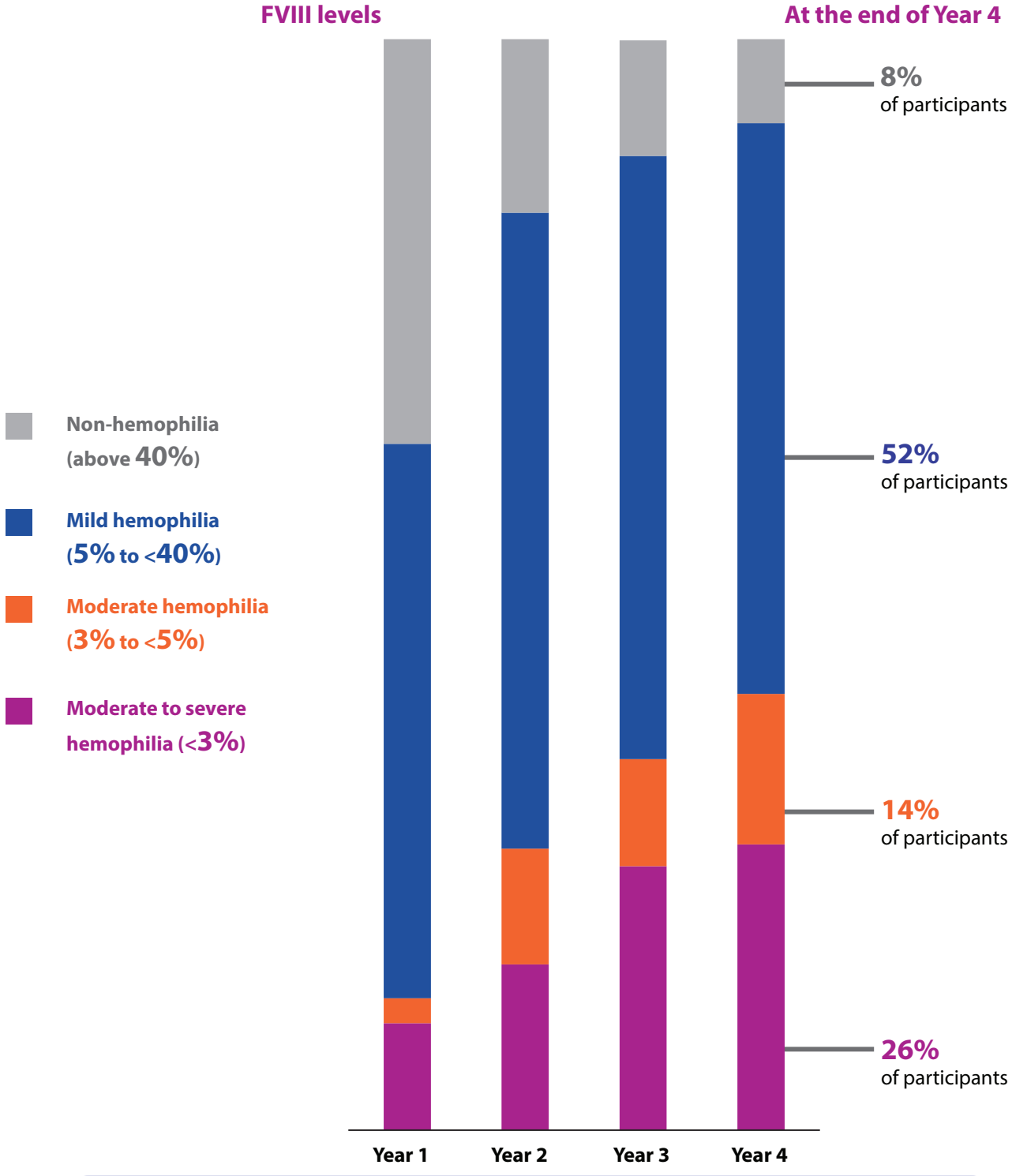
FVIII levels

Average FVIII levels were **16%** at the end of Year 4



The FVIII activity values reported here are based on the chromogenic substrate assay. If your center uses one-stage assay (also referred to as 'OSA'), please note that those values tend to be ~1.5 times higher

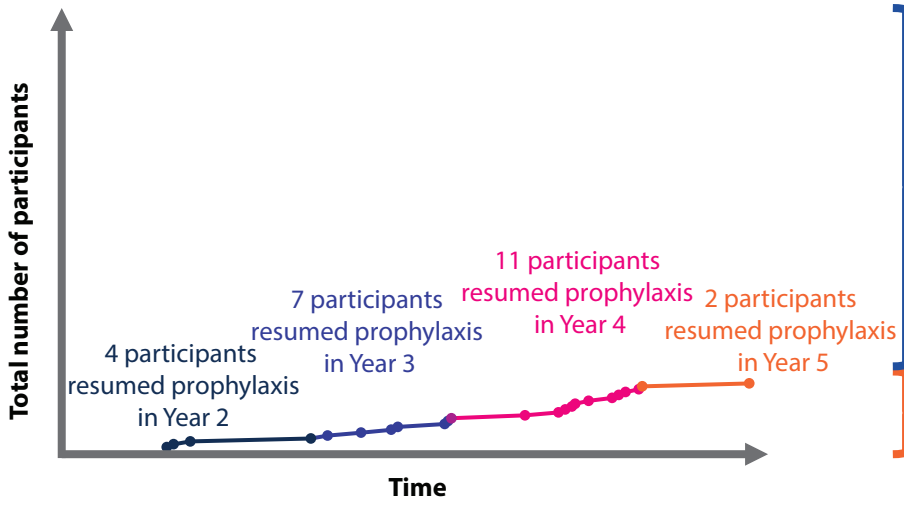
- At the end of year 4, more than half (52%) of participants had FVIII levels in the mild hemophilia range, 14% in the moderate hemophilia range, and 26% in the moderate to severe hemophilia range, while 8% had FVIII levels in the non-hemophilia range.



Because the test used to measure FVIII could not measure levels below 3%, any measurement below 3% was categorized as 'moderate to severe.' Severe hemophilia A is conventionally categorized as FVIII levels below 1%

Return to prophylaxis

- Eighteen participants started using prophylaxis since the last summary of GENEr8-1 was published in year 2, and 24 of 134 participants have returned to prophylaxis overall



110 of the 134 participants remain off prophylaxis

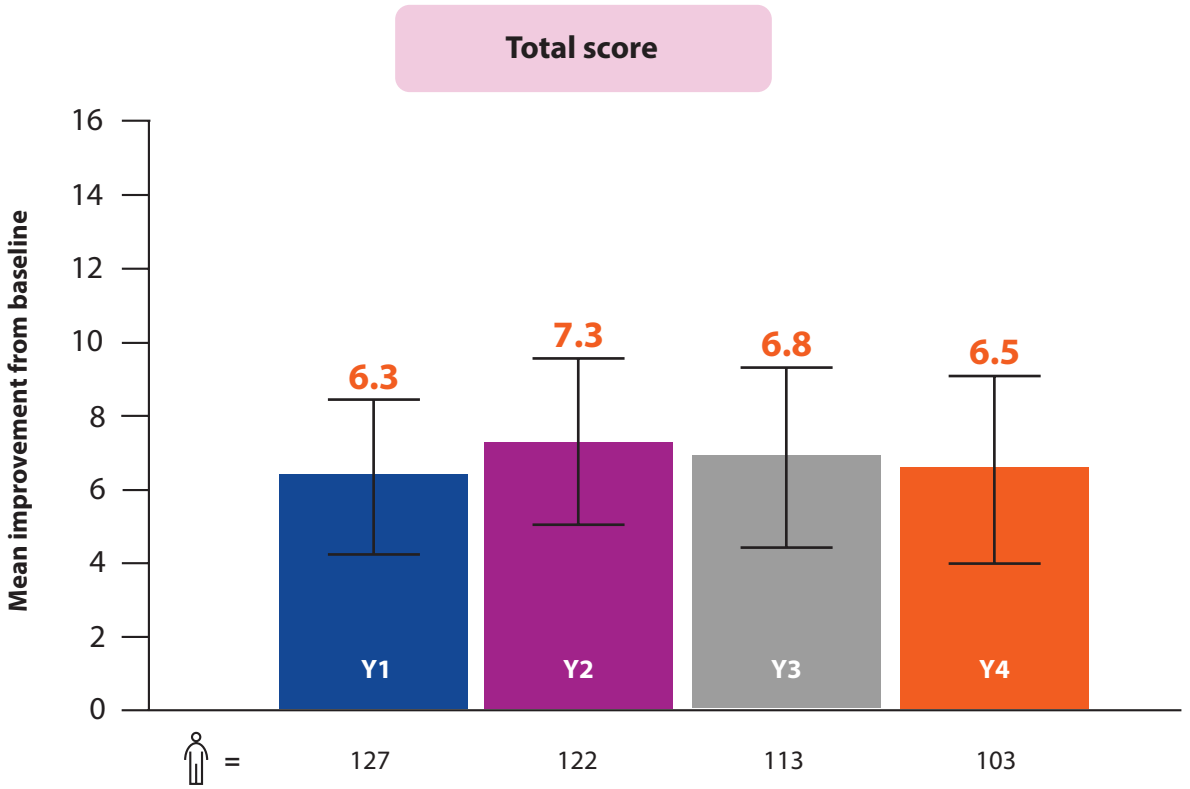
24 of the 134 participants have returned to receiving regular prophylaxis with either FVIII concentrate or emicizumab

The decision to resume prophylaxis is part of a shared decision-making process between patients and their physicians and includes many individual factors, such as the desired level of physical activity

Health-related quality of life

- At the end of year 4, the average Haemo-QOL-A Total Score was 6.5 points higher than when participants were receiving FVIII prophylaxis (higher scores represent better health-related quality of life)
- An improvement of 5.5 points in the Haemo-QOL-A Total Score is considered clinically meaningful, representing a positive change that would be meaningful to people with hemophilia
  - » For additional reading on how this threshold was determined to be clinically meaningful, please refer to this article: https://pubmed.ncbi.nlm.nih.gov/35879931/
- The improvements from baseline in Total Score at the end of years 1, 2, 3, and 4 were all considered clinically meaningful

Haemo-QOL-A is a questionnaire that measures health-related quality of life for adults with hemophilia. **A higher change from baseline indicates more improvement** in health-related quality of life



The improvements from baseline in Haemo-QOL-A Total Score at the end of Years 1, 2, 3, and 4 were all considered clinically meaningful

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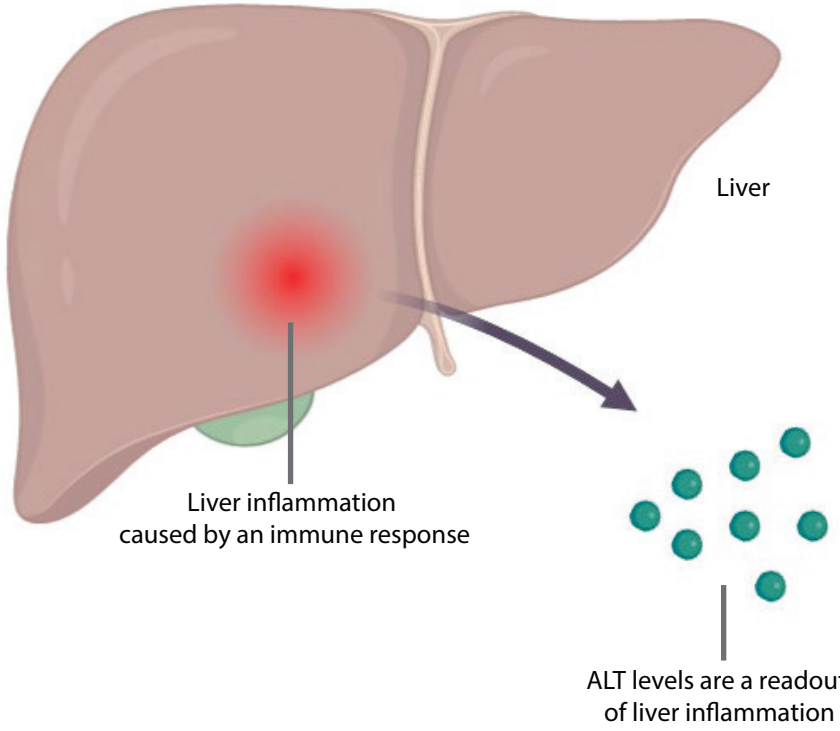
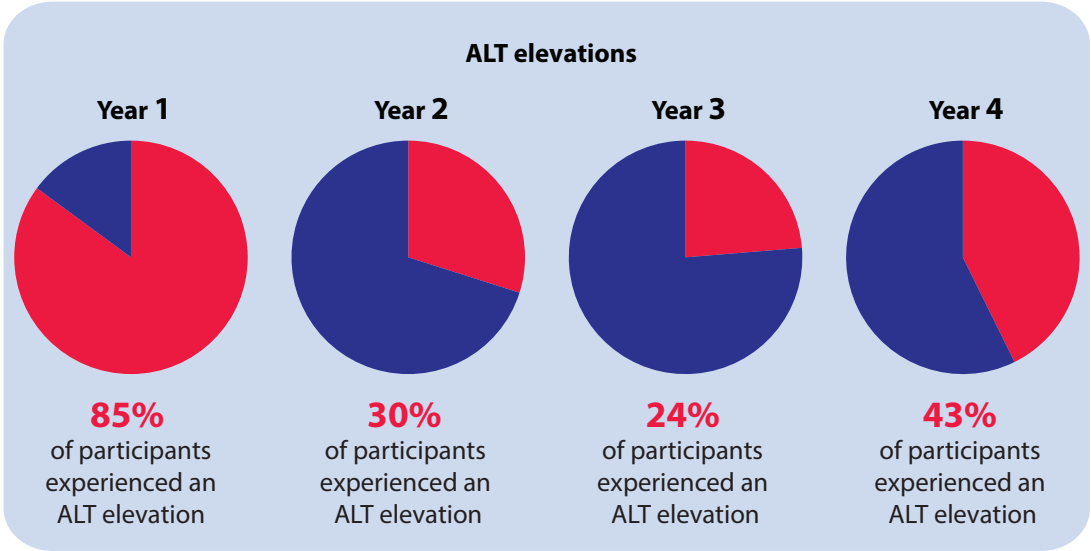
Safety results

Adverse events and immunosuppressant use

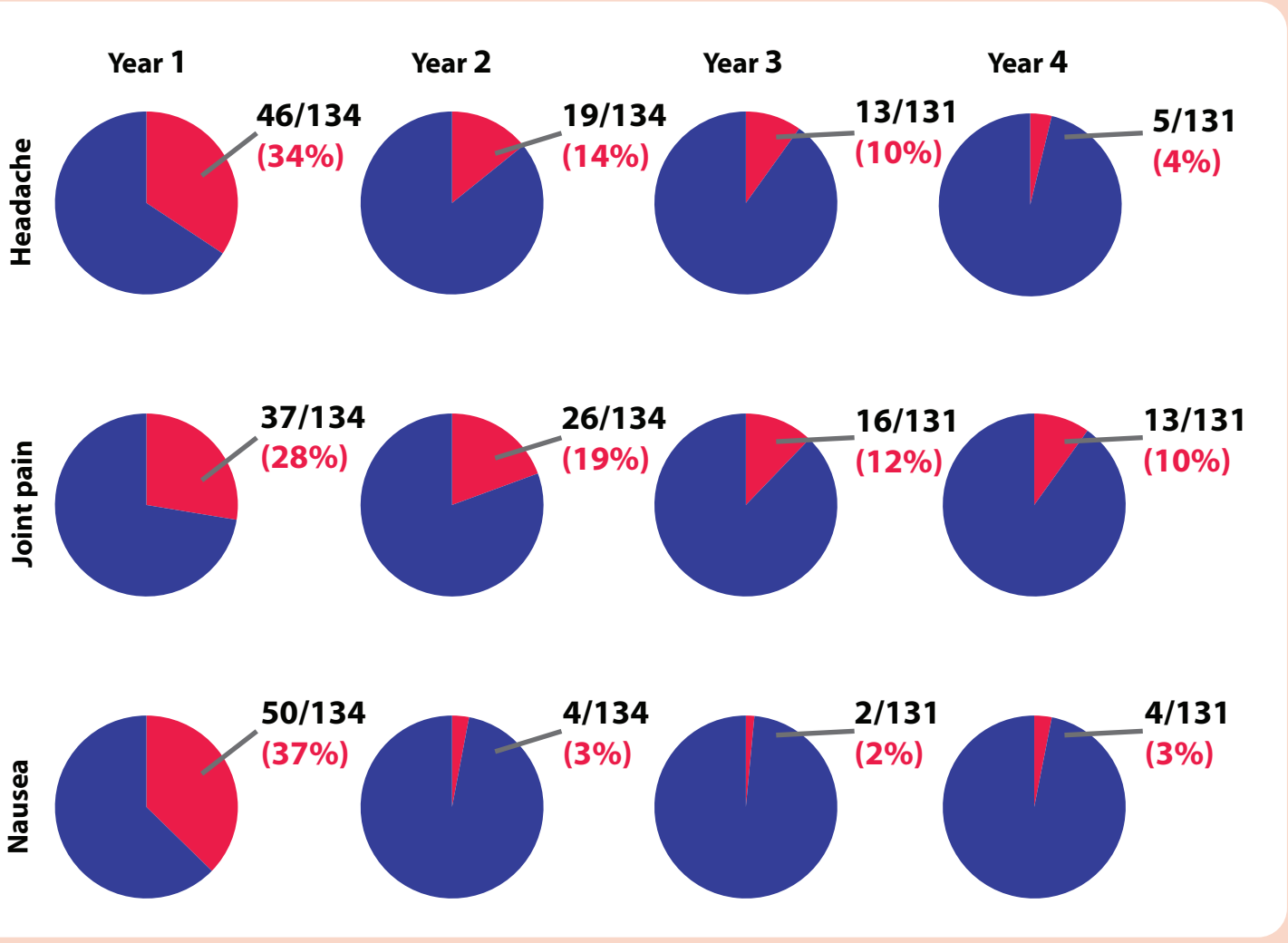
- ALT elevation can be a sign of liver inflammation. Since valoctocogene roxaparvovec targets the FVIII instructions to the liver, ALT elevations were tracked closely in GENEr8-1





This figure was created using assets from BioRender. Ghane, A. (2025) https://BioRender.com/mwtyxg1

- ALT elevations occurred in 43% of participants, but most of them were not related to treatment
  - » As an extra precaution, a low threshold for identifying an ALT elevation was chosen. Most ALT elevations were mild, with levels below the upper limit of normal but at least 1.5 times higher than a participant's baseline level
  - » None of the elevations required treatment with immunosuppressants
- Other common adverse events were headache, joint pain, and nausea



- No serious adverse events that were related to valoctocogene roxaparvovec treatment occurred after year 1
- No participants developed FVIII inhibitors, which if present, could interfere with FVIII concentrate treatment in the future
- All participants developed antibodies against the vector, which means there was an immune response against it. However, this response was not associated with a decrease in FVIII

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Tumor

What happened

- Almost 3 years after receiving valoctocogene roxaparvovec, 1 participant was diagnosed with acute lymphoblastic leukemia, a cancer of a type of white blood cell

Why it matters

- Occasionally, vector genomes become inserted into a person's regular genome
- Theoretically, if a vector genome is inserted near certain genes, it may cause a tumor to develop
- Therefore, this event was investigated thoroughly by both the study sponsor and an independent, third-party committee to determine if there was any sign the cancer was related to valoctocogene roxaparvovec

What the investigation found

- After testing cancerous and healthy cells, a known genetic error that can cause this type of cancer was found in many of the cancerous cells
- Additionally, although extremely low levels of vector genome fragments were found in some cell samples, the cancerous cells contained the lowest levels
- The independent committee found that it was unlikely that the event was related to valoctocogene roxaparvovec and did not recommend any changes to how the trial is conducted

Other things to know

- No cancers related to valoctocogene roxaparvovec have been found in any clinical trial or studies in animals
- Although some studies using animals have shown that AAV vectors can be associated with tumor development under certain conditions, no cancer related to treatment has been found in the thousands of patients who have used AAV gene therapies to treat a variety of health problems over the course of more than 20 years

Conclusions

The results of the study are encouraging because they show that valoctocogene roxaparvovec continued to provide increased protection from bleeding compared with regular FVIII prophylaxis, even after 4 years. This is shown by the large reduction in bleeding rates compared with baseline, when participants were receiving regular prophylaxis with FVIII concentrate. Additionally, most participants did not have any treated bleeds, another sign of maintained bleeding protection. Valoctocogene roxaparvovec also provided clinically meaningful health-related quality of life improvements over 4 years.

One concern with AAV-based gene therapies is that FVIII levels in some patients may drop over time, which may require returning to regular prophylactic injections. Based on results through year 2 of GENEr8-1, a statistical model was created to predict future FVIII activity levels. That model predicted that average FVIII levels at the end of year 4 would be around 14% – given that the real average was ~16%, we can reasonably expect the model, which predicts average levels of 12% at the end of year 5, to be a realistic and conservative estimate. This would suggest that many people with severe hemophilia A would have FVIII levels in the mild hemophilia range 5 years after receiving valoctocogene roxaparvovec.

No new safety concerns were found in the fourth year of the trial. The lower number of ALT elevations in year 4 and the fact that corticosteroids were not used to treat the ones that did occur are encouraging results. Overall, the risk-benefit balance of valoctocogene roxaparvovec gene therapy did not change and continues to be favorable.

Additional reading

- This summary is based on the article 'Efficacy, safety, and quality of life 4 years after valoctocogene roxaparvovec gene transfer for severe hemophilia A in the phase 3 GENEr8-1 trial,' which can be found at: https://www.rpthjournal.org/article/S2475-0379(24)00310-8/fulltext. The study began December 19, 2017, and ended November 20, 2024
- The articles reporting the 1-, 2-, and 3-year results can be found at: https://www.nejm.org/doi/full/10.1056/NEJMoa2113708, https://www.nejm.org/doi/full/10.1056/NEJMoa2211075, and https://www.jthjournal.org/article/S1538-7836(24)00184-3/fulltext, respectively
- A plain language summary of the 2-year results is available at: https://www.futuremedicine.com/doi/10.2217/frd-2023-0007
- More information about GENEr8-1 can be found at the study registration site: https://clinicaltrials.gov/ct2/show/NCT03370913

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Author contributions

All authors made significant contributions to this work, critically reviewed the manuscript, approved all versions of the manuscript, and agree to be accountable for the contents of the article. Bella Madan, Margareth C. Ozelo, Gili Kenet, Sheng-Chieh Chou, and Johnny Mahlangu are investigators on the GENEr8-1 trial who carried out the procedures, collected data, interpreted data, and provided critical input during the drafting of the manuscript. Ebony Dashiell-Aje and Tara M. Robinson contributed to the study design, data analysis, and data interpretation and provided critical input during the drafting of the manuscript. Michael Recht, Simon Fletcher, and Dor Goshen are experts in the field of hemophilia who contributed to data interpretation and provided critical input during the drafting of the manuscript. Francisco P. Careta and Andres Ruiz are lived experience experts who contributed to data interpretation and provided critical input during the drafting of the manuscript.

Disclosure statement

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