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# Plain language summary of 4-year efficacy and safety data in the GENEr8-1 trial of valoctocogene roxaparvovec, a gene therapy for severe hemophilia A

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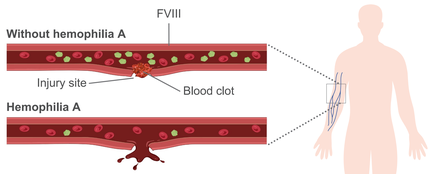
## What is hemophilia A?

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




Factor VIII

In **mild hemophilia A**, when FVIII levels are between 5% and 40% of non-hemophilia levels, 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

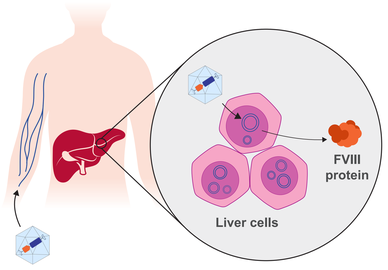
## What is valoctocogene roxaparvovec?

**Valoctocogene roxaparvovec is the first approved gene therapy for hemophilia A.** Gene therapy is meant to address the lack of genetic instructions for making FVIII


The *vector genome* contains instructions for the body to make FVIII

The *promoter* specifies that only liver cells should read the instructions

The *vector* is the empty "shell" of the *adeno-associated virus*




**FVIII is produced in the liver and circulates throughout the body**

## What is the GENEr8-1 study?

GENEr8-1 is a *phase 3 clinical trial* that is testing the *efficacy* and safety of a single dose of valoctocogene roxaparvovec

### What were the 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 many total bleeds participants experienced per year
- 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

### Who could participate in the study?

**All participants were**
- Males with severe hemophilia A
- Age 18 years or older
- Previously treated with exogenous FVIII *prophylaxis* for at least 1 year before joining

**Patients could not join the study if they had**
- Liver or kidney problems
- Antibodies to the vector
- FVIII inhibitors

## Who participated in the study?

**112** participants enrolled following an observational study of FVIII infusions in hemophilia A

**22** participants enrolled directly into GENEr8-1

All **134** participants received a single dose of **valoctocogene roxaparvovec**

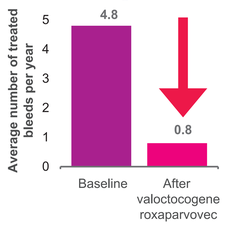
Years 1–3 after gene therapy

Year 4 after gene therapy

**129** participants are still in the study at least 4 years after the gene therapy was given

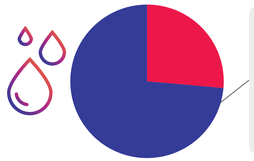
## What were the efficacy results?

### Treated bleeding



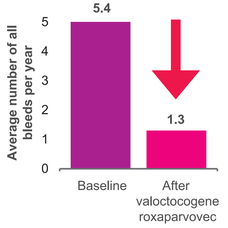

The 112 participants who joined from the observational study had **83%** fewer bleeds per year **that needed treatment** after receiving valoctocogene roxaparvovec compared with before

### Participants with no treated bleeds



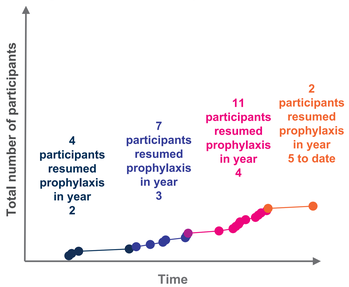
**74%** of participants who enrolled from the observational study had **no treated bleeds** during year 4

### Overall bleeding




The 112 participants who joined from the observational study had **77%** fewer bleeds per year **regardless of treatment** after receiving valoctocogene roxaparvovec compared with before

### Timing of return to prophylaxis

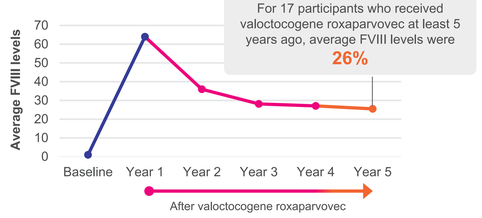



**The decision to resume prophylaxis is part of a shared decision-making process** between patients and their physicians and includes many individual factors, such as FVIII activity, bleeds, and physical activity level

### FVIII levels over time

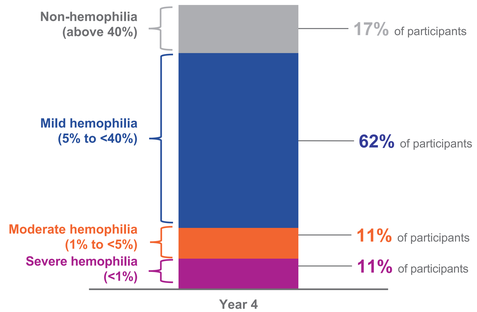
Average one-stage FVIII levels were **27%** at the end of year 4

For 17 participants who received valoctocogene roxaparvovec at least 5 years ago, average FVIII levels were **26%**




The FVIII levels reported here are based on the **one-stage assay**. If your center uses the chromogenic assay, please note that those values tend to be ~1.5 times lower

### FVIII levels at the end of year 4

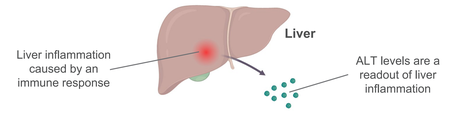



**110 participants** remain off prophylaxis. Of these, the evaluable participants had **92%** fewer treated bleeds per year after receiving valoctocogene roxaparvovec compared with before

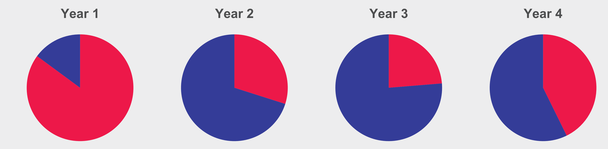
**24 participants** have returned to receiving regular prophylaxis with either FVIII concentrate or *emicizumab*. Of these, the evaluable participants had **21%** fewer treated bleeds per year from the time they received valoctocogene roxaparvovec to when they resumed prophylaxis compared with before

## What were the safety results?

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




### ALT elevations




- During year 4, **ALT elevations occurred in 43% of participants; most were mild, and none were treatment-related**. As an extra precaution, a low threshold for identifying ALT elevation was chosen
- Overall, no participants developed inhibitors, treatment-related malignancies, or dangerous blood clots from too-high FVIII
- Other common adverse events were **headache** and **joint pain,** which occurred in fewer participants during year 4 compared with earlier years. **Nausea** also occurred in consistently fewer participants in year 4 compared with year 1

## What do the results mean?

- A single infusion of valoctocogene roxaparvovec continued to provide **increased protection from bleeding** compared with regular FVIII prophylaxis after the fourth year
- **No new safety concerns** were found in the fourth year of the trial
- Overall, the **risk-benefit balance was unchanged** after the fourth year of the trial

## Glossary

***Adeno-associated virus:*** 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

***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

***ALT (alanine aminotransferase):*** an enzyme (a type of protein) that is commonly monitored by doctors as a sign of liver inflammation

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

***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

***FVIII (factor VIII):*** a critical protein for blood clotting. FVIII is produced by reading the instructions in the *F8* gene

***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

***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

***Prophylaxis:*** a treatment aimed at preventing an event from occurring

***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

***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

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