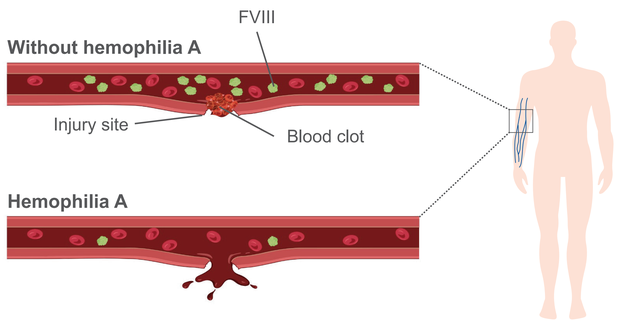
How long do the effects of valoctocogene roxaparvovec last?
A plain language summary of a model estimating how long patients with hemophilia A may experience benefit

Sandra Santos[1], Tara M. Robinson[2], Felipe Rico[2], David Trueman[3], Sean Jeffrey[4]

[1]BioMarin UK Ltd., London, UK; [2]BioMarin Pharmaceutical Inc., Novato, CA, USA; [3]Source Health Economics, London, UK; [4]Patient Author, Missoula, MT, USA

What is hemophilia A?

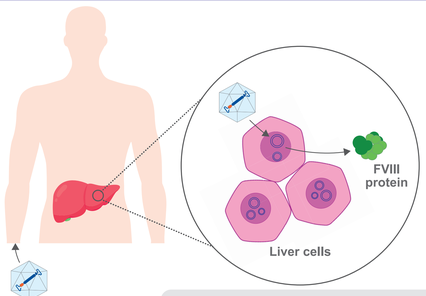
Hemophilia A is an inherited disorder that causes people to bleed easily because they have lower-than-normal levels of ***FVIII*** (factor VIII; "factor eight"), a protein that is needed for normal blood clotting



In **severe hemophilia A**, when FVIII levels are less than 1% of healthy levels, bleeding occurs even with no apparent injury (called "spontaneous bleeding"), 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 correct genetic instructions for making FVIII



FVIII is produced in the liver and circulates throughout the body

Valoctocogene roxaparvovec uses an empty viral "shell" that is based on an *adeno-associated virus* to transfer genetic instructions for making FVIII

In clinical trials, **a single infusion of valoctocogene roxaparvovec has been found to significantly reduce the number of bleeding episodes** in adult men with severe hemophilia A compared to their prior treatment with FVIII *prophylaxis*

What was the aim of this analysis?

To estimate **how long the beneficial effects of valoctocogene roxaparvovec treatment may last** (the "durability of treatment effect") using the most recent data from clinical trials

How was this analysis performed?

GENEr8-1:

- A *phase 3 clinical trial* testing the efficacy and safety of a single dose of valoctocogene roxaparvovec

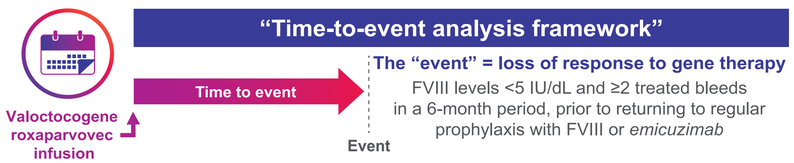
134 participants received valoctocogene roxaparvovec ($6x10^{13}$ vector genomes per kilogram body weight)
4–5 years ago

270-201:

- A phase 1/2 clinical trial testing the safety, side effects, and best dose of valoctocogene roxaparvovec

7 participants received valoctocogene roxaparvovec ($6x10^{13}$ vector genomes per kilogram body weight)
7 years ago

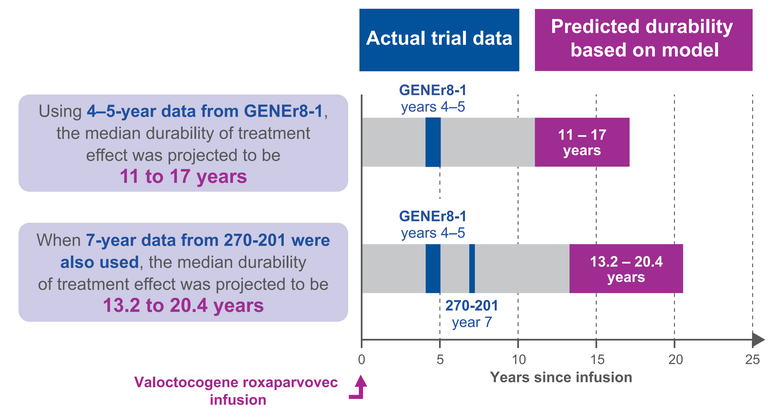
Using the 4–5 year data from GENEr8-1 and the 7-year data from 270-201, the durability of treatment effect was estimated using a "time-to-event analysis framework" in which loss of response data observed from the clinical trials were extrapolated using different parametric survival distributions. This provided a range of estimates for the predicted durability of treatment effect



What did this analysis find?

Using **4–5-year data from GENEr8-1**, the median durability of treatment effect was projected to be
11 to 17 years

When **7-year data from 270-201 were also used**, the median durability of treatment effect was projected to be
13.2 to 20.4 years



What do the results mean?

- This time-to-event analysis framework provides **a better understanding of how the current trial data will look in the future**
- Patients with severe hemophilia A might **continue to benefit from gene therapy with valoctocogene roxaparvovec beyond the 4–7 years of follow-up data collected in clinical trials** to date

Glossary

Adeno-associated virus: commonly referred to as "AAV", this virus 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

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

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

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

Median: the middle value of an ordered list of numbers. Half of the participants have a value higher than the median, and half have a value lower than the median

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

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

Prophylaxis: a treatment for hemophilia A aimed at preventing a bleeding 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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