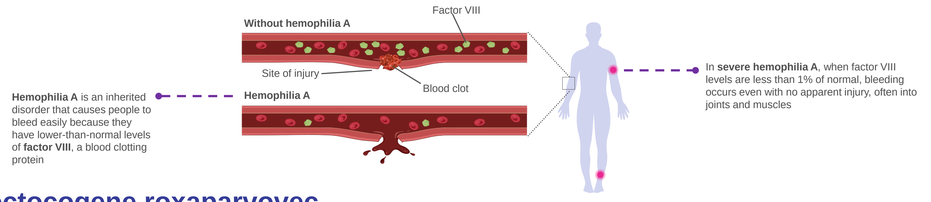
CR8

Effects of valoctocogene roxaparvovec gene therapy in people with severe hemophilia A after 3 years

Gillian Lowe[1], Patrick James Lynch[2], Johnny Mahlangu[3], Margareth C Ozelo[4], **Brian O'Mahony**[5], Tara M Robinson[6], Hua Yu[6], Leonard A Valentino[7]

[1]University Hospitals Birmingham NHS Foundation Trust, UK; [2]Believe Ltd, Hawthorne, CA, USA; [3]University of Witwatersrand and NHLS, Johannesburg, South Africa; [4]University of Campinas, Sao Paolo, Brazil; [5]Irish Haemophilia Society and Trinity College Dublin, Dublin, Ireland; [6]BioMarin Pharmaceutical Inc., Novato, CA, USA; [7]Rush University, Chicago, IL, and National Hemophilia Foundation, New York, NY, USA

Hemophilia A

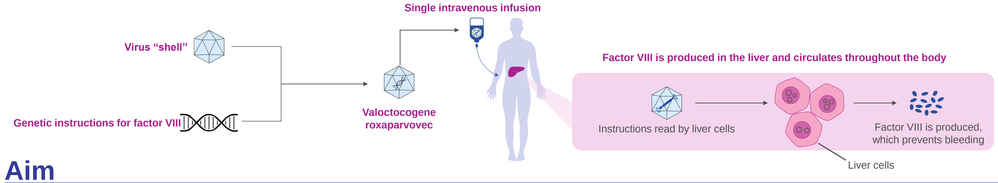


Hemophilia A is an inherited disorder that causes people to bleed easily because they have lower-than-normal levels of **factor VIII**, a blood clotting protein

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

Valoctocogene roxaparvovec

- Valoctocogene roxaparvovec, a gene therapy, helps prevent bleeding by providing the body with genetic instructions for making factor VIII inside the "shell" of the adeno-associated virus[2,3]



Aim

- **To determine how well valoctocogene roxaparvovec works to prevent bleeding and how safe it is 3 years into the phase 3 GENEr8-1 trial**

GENEr8-1

- In the phase 3 GENEr8-1 trial, 134 adult men with severe hemophilia A were given a single infusion of valoctocogene roxaparvovec
  - The infusion delivered 6x10^{13} (that's 60,000,000,000,000) copies of the factor VIII instructions for every kilogram of participant weight

GENEr8-1 participants

112 participants joined from another 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 → Year 2 → Year 3

131 participants are still in the study 3 years after the gene therapy was given

All participants were
- Male with severe hemophilia A
- Age 18 or older
- Previously treated with factor VIII for at least 1 year before joining
- Previously treated with factor VIII on at least 150 separate days
- Factor VIII inhibitor–free (antibodies that target factor VIII)

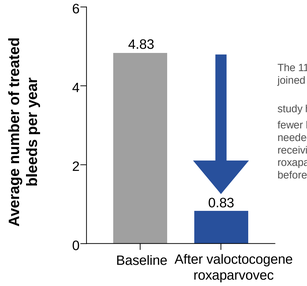
Patients could not join the study if they had
- Weakened immune systems
- Substantial problems with liver structure or function
- Low platelet counts
- Kidney problems
- An immune response to the "shell" in which the factor VIII instructions are packaged

Assessments

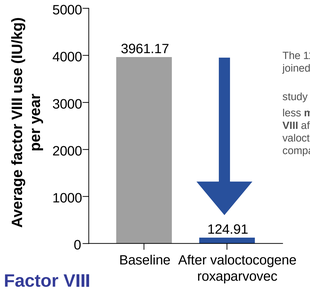
To see how well valoctocogene roxaparvovec prevents bleeding
- How many bleeds participants experienced per year that needed to be treated with factor VIII
- How much manufactured factor VIII participants had to use
- How much factor VIII the participants were making

To see how many side effects valoctocogene roxaparvovec causes
- How often the body showed signs of fighting foreign substances in the liver
- How often participants needed to use steroids to manage liver problems
- How often any side effects occurred after valoctocogene roxaparvovec infusion

Bleeding



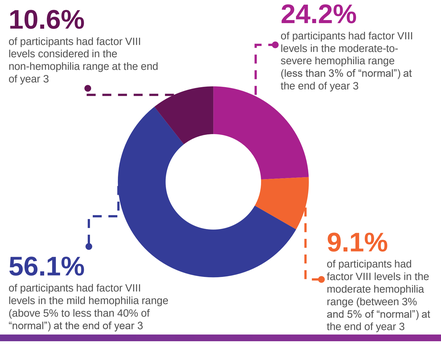
The 112 participants who joined from the separate study had **82.9%** fewer **bleeds per year** that needed treatment after receiving valoctocogene roxaparvovec compared with before



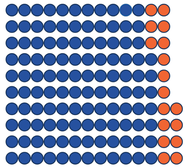
The 112 participants who joined from the separate study used **96.8%** less **manufactured factor VIII** after receiving valoctocogene roxaparvovec compared with before

Factor VIII

- On average, participants' factor VIII levels were **18.4%** of "normal" at the end of year 3[1]



Return to factor VIII prophylaxis



So far, **17** out of 131 participants still in the study have returned to getting regular **prophylactic factor VIII infusions**

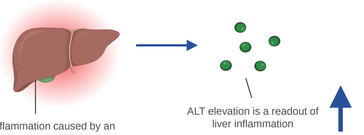
Quality of Life

- Participants were asked to fill out a questionnaire designed to measure quality of life specifically for people with hemophilia A (**Haemo-QoL-A Total Score**)
- Participants' answers on the questionnaire showed their **quality of life increased** by a meaningful amount[4]

Safety

- By year 3, all 134 participants had experienced at least 1 side effect
- Because valoctocogene roxaparvovec targets the factor VIII instructions to the liver, monitoring liver health is especially important in the GENEr8-1 trial
  - Levels of an enzyme called alanine aminotransferase (commonly referred to as **ALT**) were measured to see if the body is fighting foreign substances in the liver (called "inflammation")

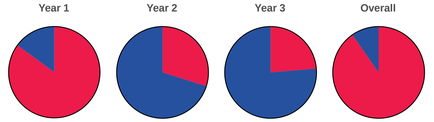
ALT elevations



Liver inflammation caused by an immune response to valoctocogene roxaparvovec or the newly made factor VIII

ALT elevation is a readout of liver inflammation

Proportion of participants with ALT elevation



85.1% of participants experienced an ALT elevation during year 1

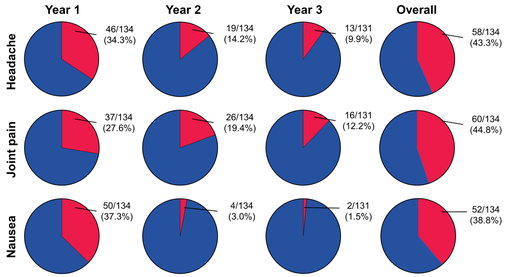
29.9% of participants experienced an ALT elevation during year 2

23.7% of participants experienced an ALT elevation during year 3

90.3% of participants experienced an ALT elevation overall

Other side effects

- Other common side effects included headache, joint pain, and nausea (the proportion of participants who experienced each side effect is shown in red)



Conclusions

- The GENEr8-1 trial evaluated how well valoctocogene roxaparvovec gene therapy prevented bleeding that needed factor VIII treatment, increased factor VIII levels, and reduced factor VIII use in men with severe hemophilia A
- Side effects—such as liver inflammation—were monitored to assess the safety of valoctocogene roxaparvovec gene transfer
- Valoctocogene roxaparvovec decreased the average number of treated bleeds and amount of factor VIII used through 3 years after a single infusion
- The most common side effect during year 3 was still ALT elevation
- For more information about GENEr8-1, visit the trial registration website at https://clinicaltrials.gov/ct2/show/NCT03370913

Glossary

Adeno-associated virus: Commonly referred to as "AAV", this virus does not cause disease in humans and can be used to deliver genetic material to specific parts of the body
Alanine aminotransferase: Also referred to as "ALT", this enzyme is commonly used by doctors to test for liver inflammation because its levels go up when there is inflammation in the liver
Factor VIII: A protein that is crucial for forming blood clots
Participant: A person who meets the criteria to be included in the study and chose to take part
Phase 3 trial: After finding the most effective safe dose in the phase 1 and 2 trials, phase 3 trials determine if the benefits of the treatment outweigh the risks and if the treatment works better than a currently approved treatment in a larger group of people
Prophylaxis: A treatment aimed at preventing an event from occurring
Side effect: Also known as an "adverse event", these are health-related events that occur after a participant receives a treatment. Not all side effects are related to the study treatment and may be incidental

References

1. Srivastava A, et al. *Haemophilia.* 2020;26:1–158. **2.** Ozelo M, et al. *N Engl J Med.* 2022;386:1013–25. **3.** Mahlangu J, et al. *N Engl J Med.* 2023;388:694–705. 4. Quinn J, et al. *Patient Relat Outcome Meas.* 2022;13:169–80.

Disclosures

BOM has received consulting fees from BioMarin Pharmaceutical Inc. and Freeline. **GL** has received honoraria for participating in educational events from Alexion, LEO, Novartis, Novo Nordisk, Sanofi, Sobi, and Takeda; and consulting fees from UCB. **MCO** reports consulting fees from Bayer, BioMarin Pharmaceutical Inc., Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; research grants from Pfizer, Roche, and Takeda; service as a clinical trial investigator for BioMarin Pharmaceutical Inc., Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; speaker honoraria from Bayer, BioMarin Pharmaceutical Inc., Novo Nordisk, Roche, and Takeda; travel support from Novo Nordisk, Roche, and Takeda; and participation in grant reviewing for Grifols. **JM** reports consulting fees from Baxalta, CSL Behring, Catalyst Biosciences, Freeline, LFB, Novo Nordisk, and Spark; research grants from and service as a clinical trial investigator for BioMarin Pharmaceutical Inc., CSL Behring, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Sobi, and Unique; and speaker fees from Novo Nordisk, Pfizer, Roche, Sanofi, Sobi, Shire, Takeda, the International Society on Thrombosis and Haemostasis, and the World Federation of Hemophilia. **TR** and **HY** are employees and shareholders of BioMarin Pharmaceutical Inc. **PJL** and **LAV** have no conflicts to declare.

Funding

GENEr8-1 is funded by BioMarin Pharmaceutical Inc.

Acknowledgements

We thank all trial participants, investigators, and site staff. Medical writing support was provided by M Amin Ghane, PhD of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc.

Presented at the National Hemophilia Foundation Bleeding Disorders Conference 2023: August 17–19, National Harbor, Maryland, USA