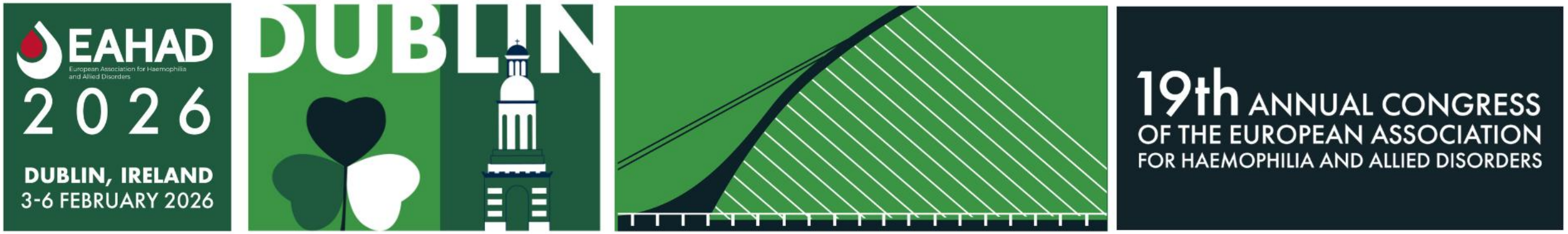

Characterization of ALT elevations during the 5-year GENEr8-1 trial of valoctocogene roxaparvovec gene transfer for severe hemophilia A

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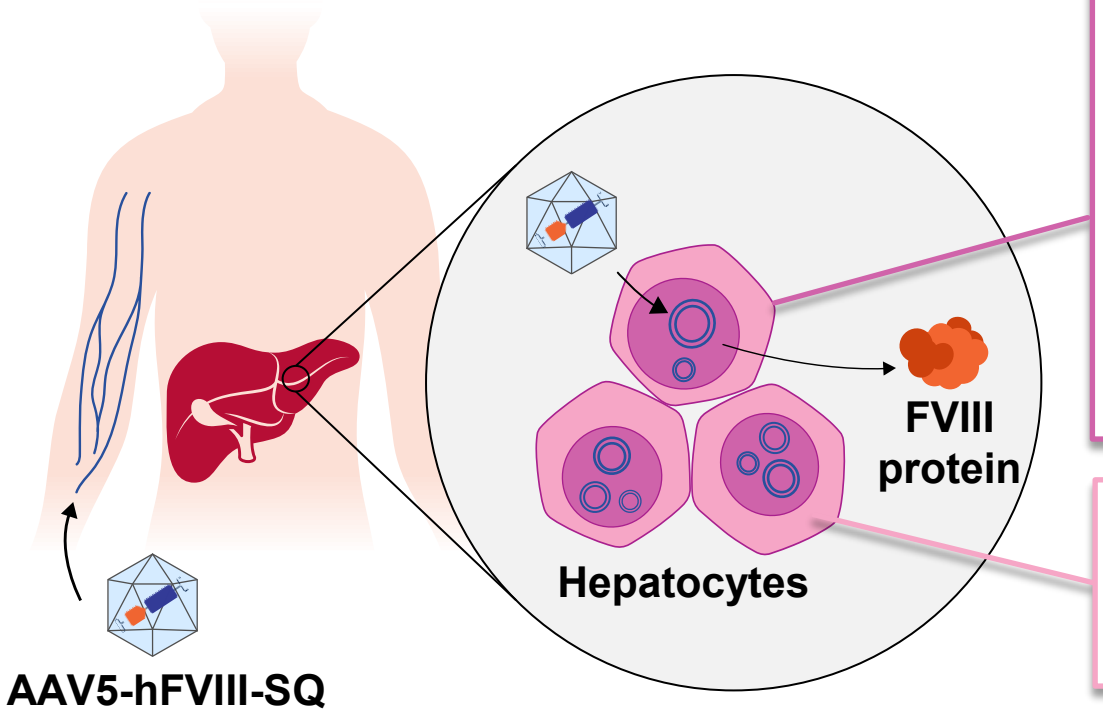
Disclosure for Robert Klamroth

In compliance with COI policy, EAHAD requires the following disclosures to the session audience:

Shareholder	No relevant conflicts of interest to declare.
Grant / Research Support	Bayer, CSL Behring, and LEO Pharma
Consultant	Bayer, BioMarin Pharmaceutical Inc., CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai Pharmaceutical, Sanofi, Sobi, and Takeda
Employee	No relevant conflicts of interest to declare.
Paid Instructor	No relevant conflicts of interest to declare.
Speaker Bureau	No relevant conflicts of interest to declare.
Other	Bayer, BioMarin Pharmaceutical Inc., Biotest, CSL Behring, Daiichi Sankyo, Grifols, LEO Pharma, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai Pharmaceutical, Sanofi, Shire/Takeda, Sobi, and uniQure

Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a B-domain-deleted FVIII coding sequence to enable FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1]



ALT is released during hepatocyte breakdown and indicates liver damage[2]

Elevated ALT can be caused by many different external factors, such as

- Infection
- Alcohol use
- Certain medications

ALT elevations may occur in transduced hepatocytes after AAV gene therapy, hypothesized to be due to immune-mediated damage[3]

AAV5, adeno-associated virus serotype 5; ALT, alanine aminotransferase; FVIII, factor VIII; hFVIII-SQ, B-domain-deleted human FVIII, SQ variant.

1. Ozelo MC, et al. *N Engl J Med*. 2022;386:1013–1025 **2.** Oh RC, et al. *Am Fam Physician*. 2017;96:709–715 **3.** Mucke MM, et al. *J Hepatol*. 2024;80:352–361

GENEr8-1 trial investigated outcomes for 5 years after gene transfer

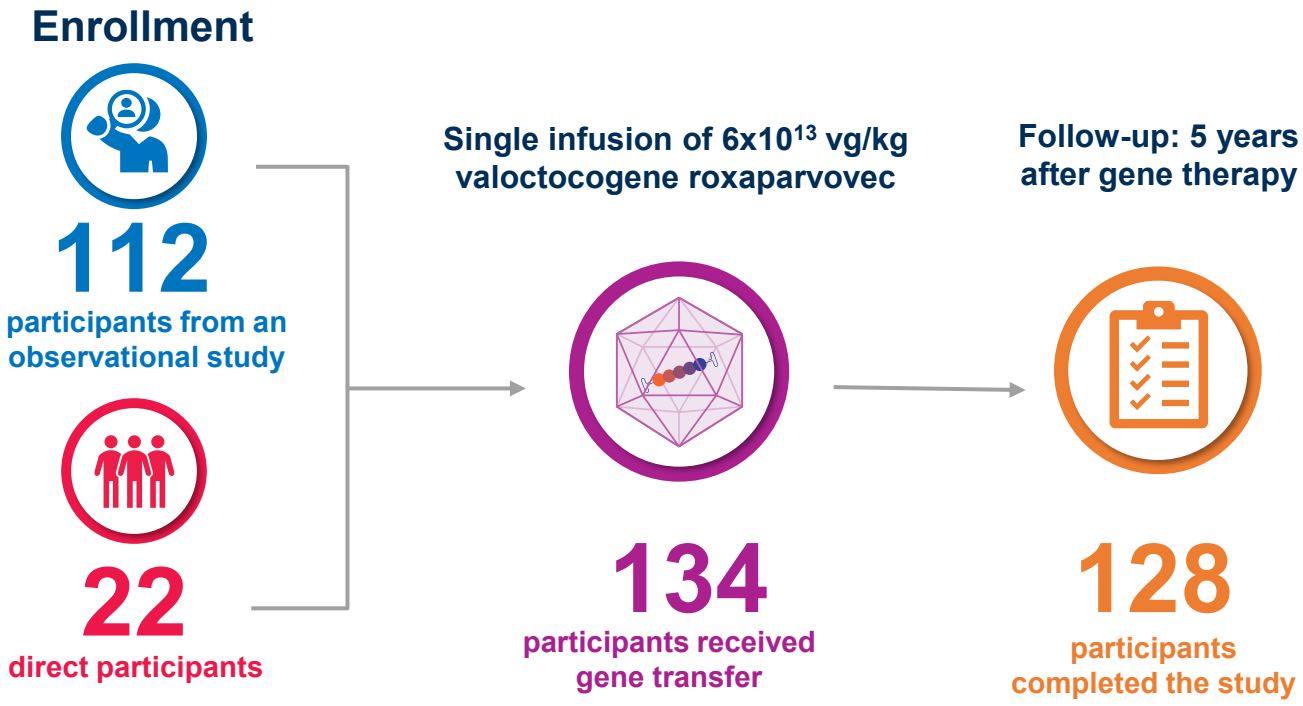
- GENEr8-1 was an open-label, phase 3 trial (NCT03370913)
- Participants who received a single infusion of valoctocogene roxaparvovec had improved protection from bleeds compared with those who received regular FVIII prophylaxis for a period of 5 years[1]
- The most common adverse event was asymptomatic, transient ALT elevation[1]

All participants were

- Male with severe hemophilia A
- Aged 18 years or older
- Previously treated with FVIII prophylaxis for at least 1 year before joining the trial

Patients could not join the study if they had

- Weakened immune system
- Liver problems
- A pre-existing immune response to the carrier
- FVIII inhibitors

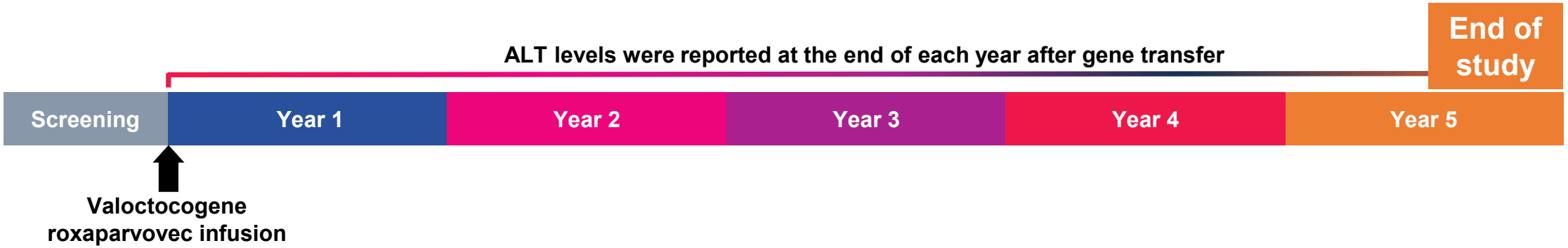


ALT, alanine aminotransferase; FVIII, factor VIII.

1. Leavitt AD, et al. *Res Pract Thromb Haemost*. In revision. 2025

ALT levels were monitored for 5 years after gene transfer

ALT elevation was the most common adverse event in GENEr8-1. Therefore, we performed a post hoc analysis characterizing ALT elevations in the 5-year period after gene transfer in terms of number, severity, timing, and the use of glucocorticoids



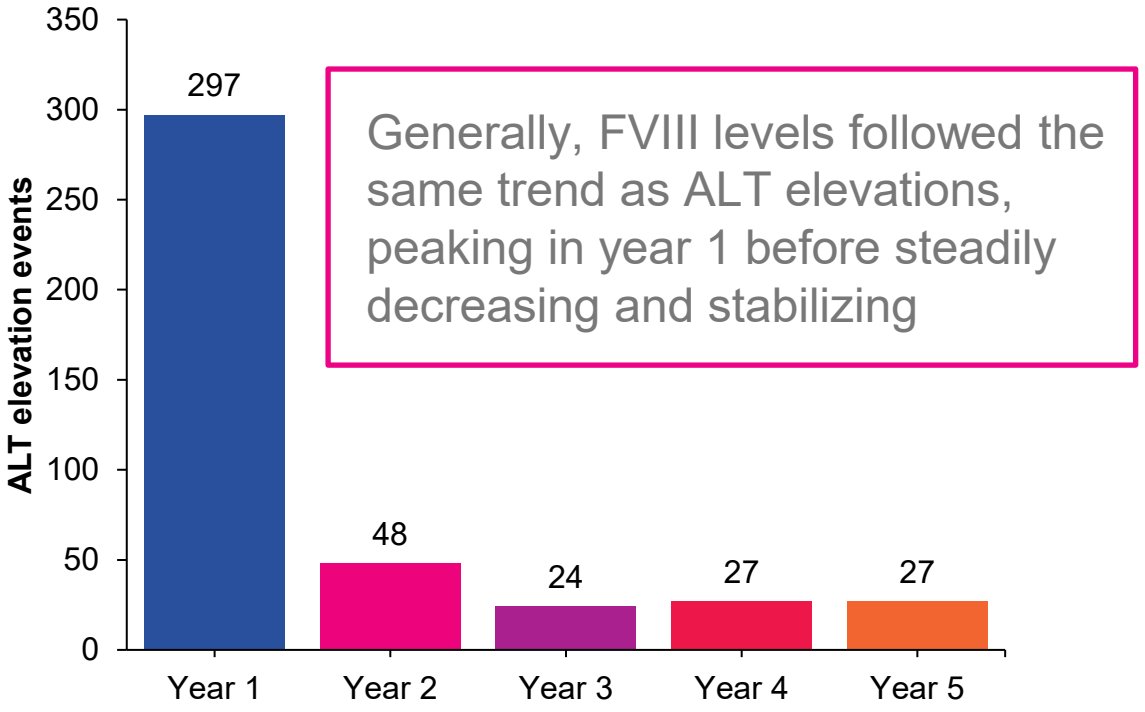
- This analysis focused on ALT elevations above the ULN (43 U/L) per central laboratory readings[1]
- The duration of an ALT elevation event was considered from onset >ULN to next measurement <ULN
- Glucocorticoids were used reactively for ALT elevation at the investigator's discretion

ALT, alanine aminotransferase; LTFU, long-term follow-up; ULN, upper limit of normal.

1. Madan B, et al. *JTH*. 2024;22:1880–1893.

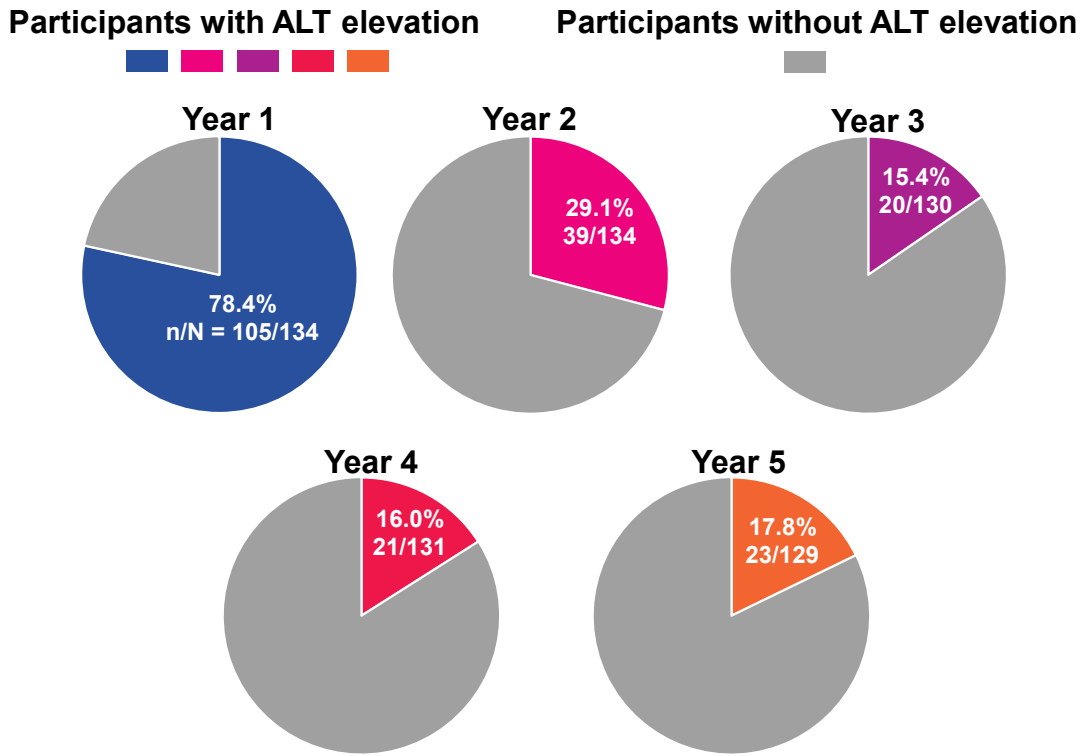
ALT elevations were most frequent in the first year after gene transfer before decreasing and stabilizing

ALT elevation events[a]



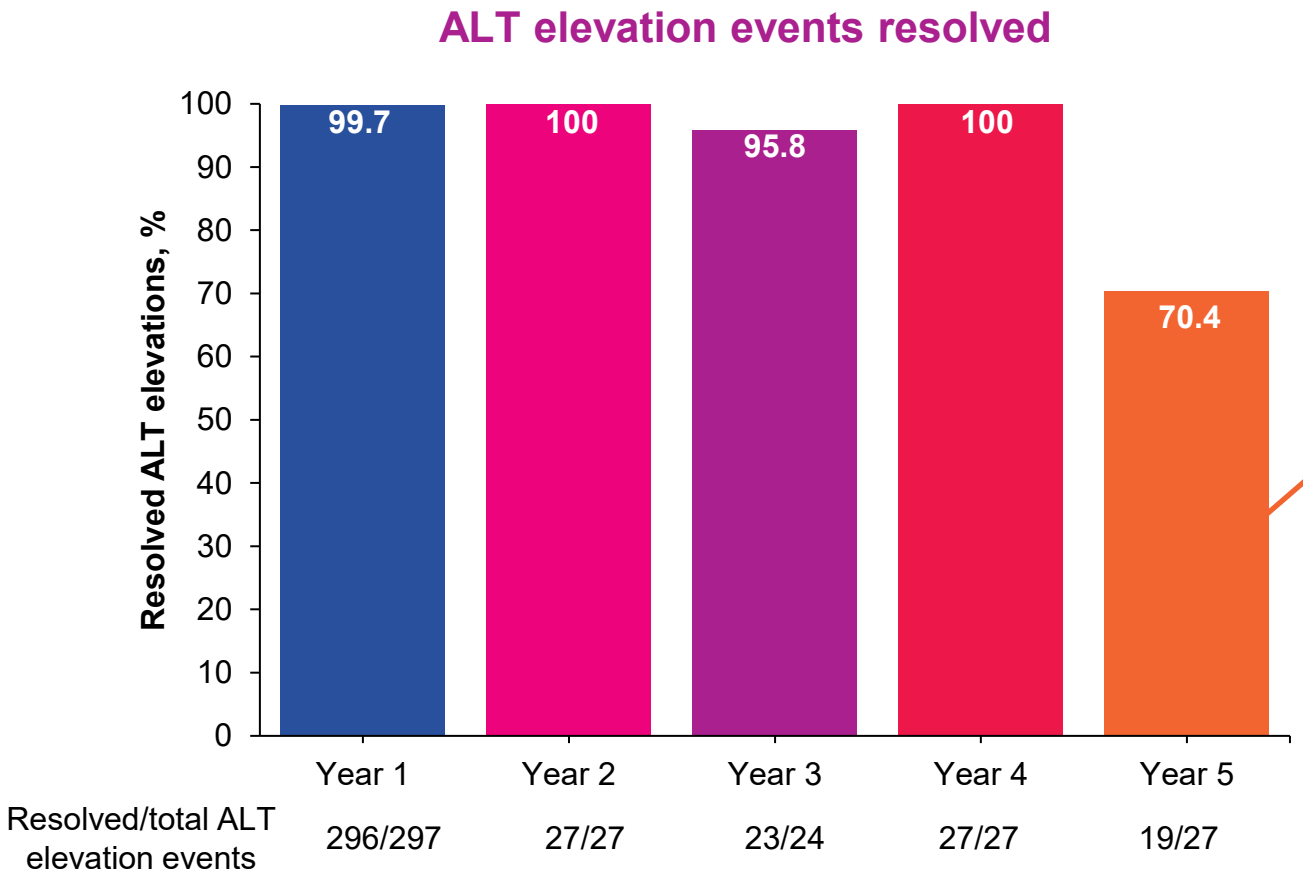
Generally, FVIII levels followed the same trend as ALT elevations, peaking in year 1 before steadily decreasing and stabilizing

Proportion of participants with ≥1 ALT elevation per year



ALT, alanine aminotransferase; FVIII, factor VIII; ULN, upper limit of normal.
[a]The duration of an ALT elevation event was considered from onset >ULN to next measurement <ULN

Most ALT elevations were transient and resolved

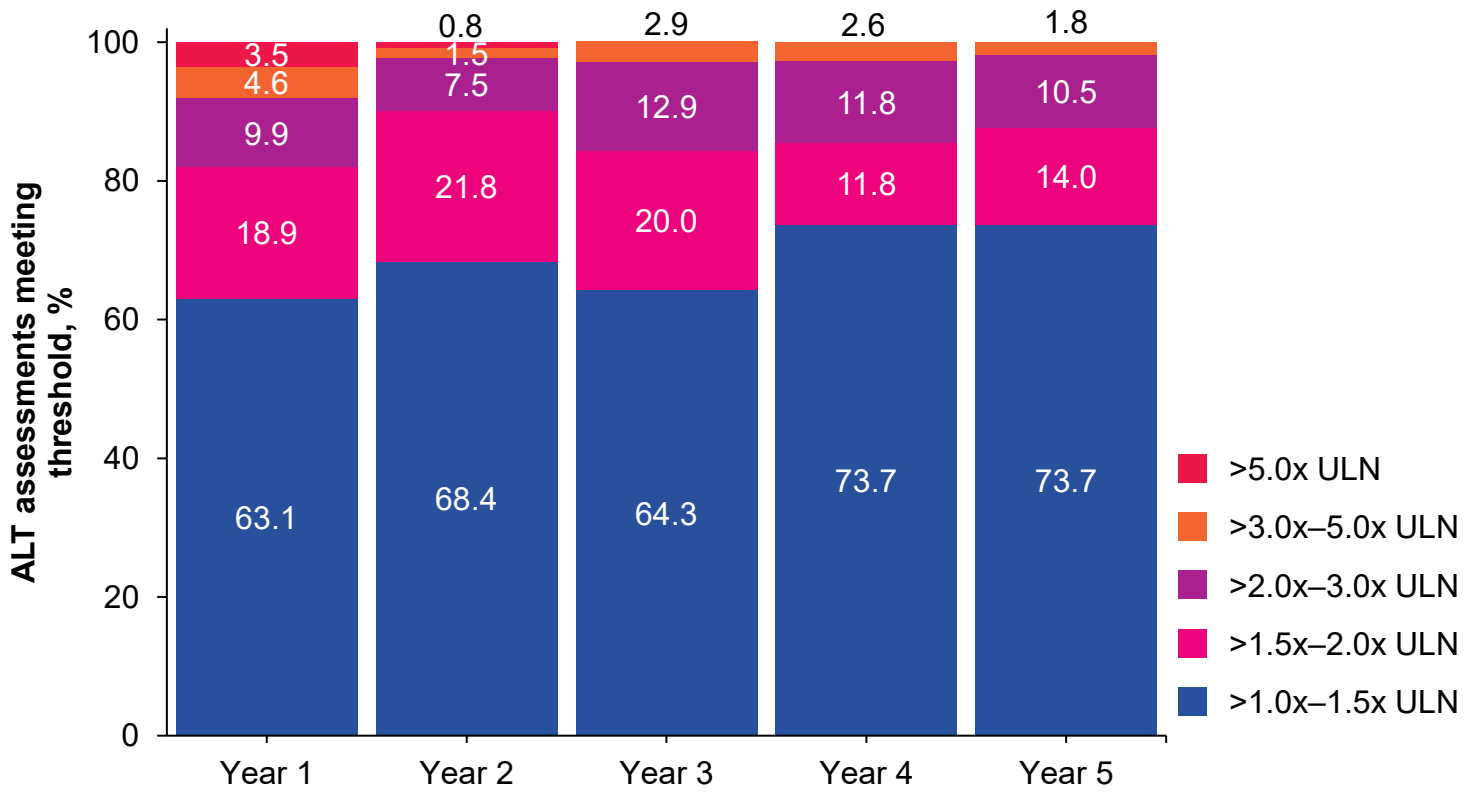


- At the end of year 5, 8 ALT elevation events were unresolved. ALT elevation events were classified as unresolved possibly due to the data cutoff date
- **Confounding factors** were identified in 4 of 8 unresolved ALT elevation events
  - Hepatic steatosis (n = 2)
  - Concurrent viral infection (n = 1)
  - B-cell leukemia[a] and prior stem cell transplant (n = 1)

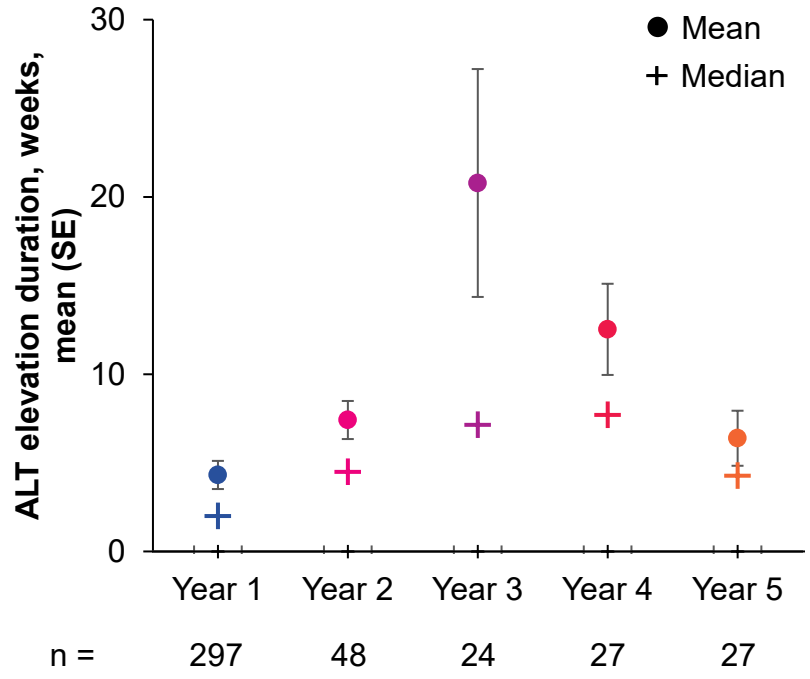
ALT, alanine aminotransferase.
[a]Previously reported malignancy.

Most ALT elevations across 5 years were mild; durations of individual ALT elevations were variable and dependent on timing of re-test

ALT elevation severity



Duration of ALT elevation[a]

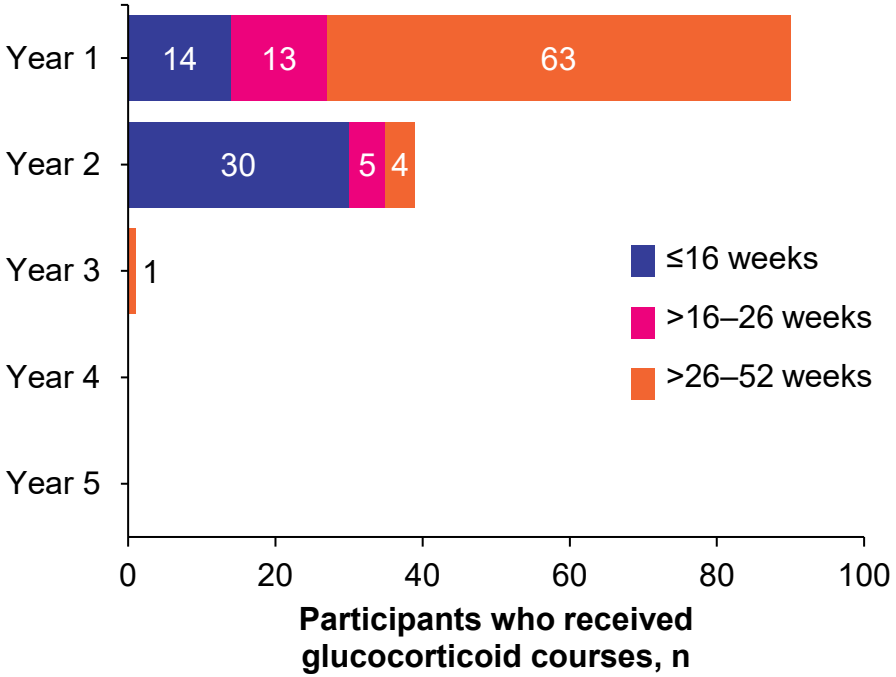


ALT, alanine aminotransferase; ULN, upper limit of normal.

[a]Duration of an ALT elevation event was considered from onset >ULN to next measurement <ULN. Allocation of each ALT elevation duration is based on the start date of the abnormal assessment.

Glucocorticoids for ALT elevations were used almost exclusively in years 1 and 2 after gene transfer

Duration of glucocorticoid use



Glucocorticoid use for ALT elevations >ULN

	Year 1 (N = 105)	Year 2 (N = 39)	Year 3[a] (N = 20)	Year 4 (N = 21)	Year 5 (N = 23)	Overall[b] (N = 111)
Used glucocorticoids for ALT elevation, n (%)	90 (85.7)	39 (100)	1 (5.0)	0	0	91 (82.0)
Total duration, days, median (min, max)	233.0 (46, 351)	53.0 (1, 349)	231.0 (231, 231)	-	-	235.0 (22, 841)
Total dose, mg, median (min, max)	6842.5 (1225, 25,110)	890.0 (1, 9040)	1515.0 (1515, 1515)	-	-	6980.0 (1225, 31,760)

ALT, alanine aminotransferase; max, maximum; min, minimum; ULN, upper limit of normal.
[a]No participants initiated glucocorticoids after year 2.
[b]Duration of glucocorticoids is the derived number of days participants were on glucocorticoids. Total dose is the total amount of corticosteroid usage. The summary statistics provided in the table were based on participants who used glucocorticoids.

Conclusions

In the 5 years after gene transfer, ALT elevation events and subsequent glucocorticoid use peaked in the first year before decreasing and stabilizing

Most ALT elevations were mild in severity and resolved; after year 2, no elevations >5x ULN occurred and no participants initiated glucocorticoids

A long-term follow-up study on the long-term efficacy and safety of valoctocogene roxaparvovec is ongoing

ALT, alanine aminotransferase; ULN, upper limit of normal.

Acknowledgments

- Thank you to all co-authors: Andrew D. Leavitt, Flora Peyvandi, Steven W. Pipe, Johannes Oldenburg, Konstantia-Maria Chavele, Gillian E. Clague, Karen Gu, Haley Sutton, and Vincenzo La Mura

- **Thank you to all trial participants, their families, study-site personnel, and investigators**
- Funding for the GENEr8-1 trial was provided by BioMarin Pharmaceutical Inc.
- Medical writing support was provided by Morgan Engelhart Wynn, PhD, of Red Nucleus, and funded by BioMarin Pharmaceutical Inc.

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