Safety and efficacy of valoctocogene roxaparvovec in participants with active or prior FVIII inhibitors: Results from a phase 1/2 trial

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Disclosures

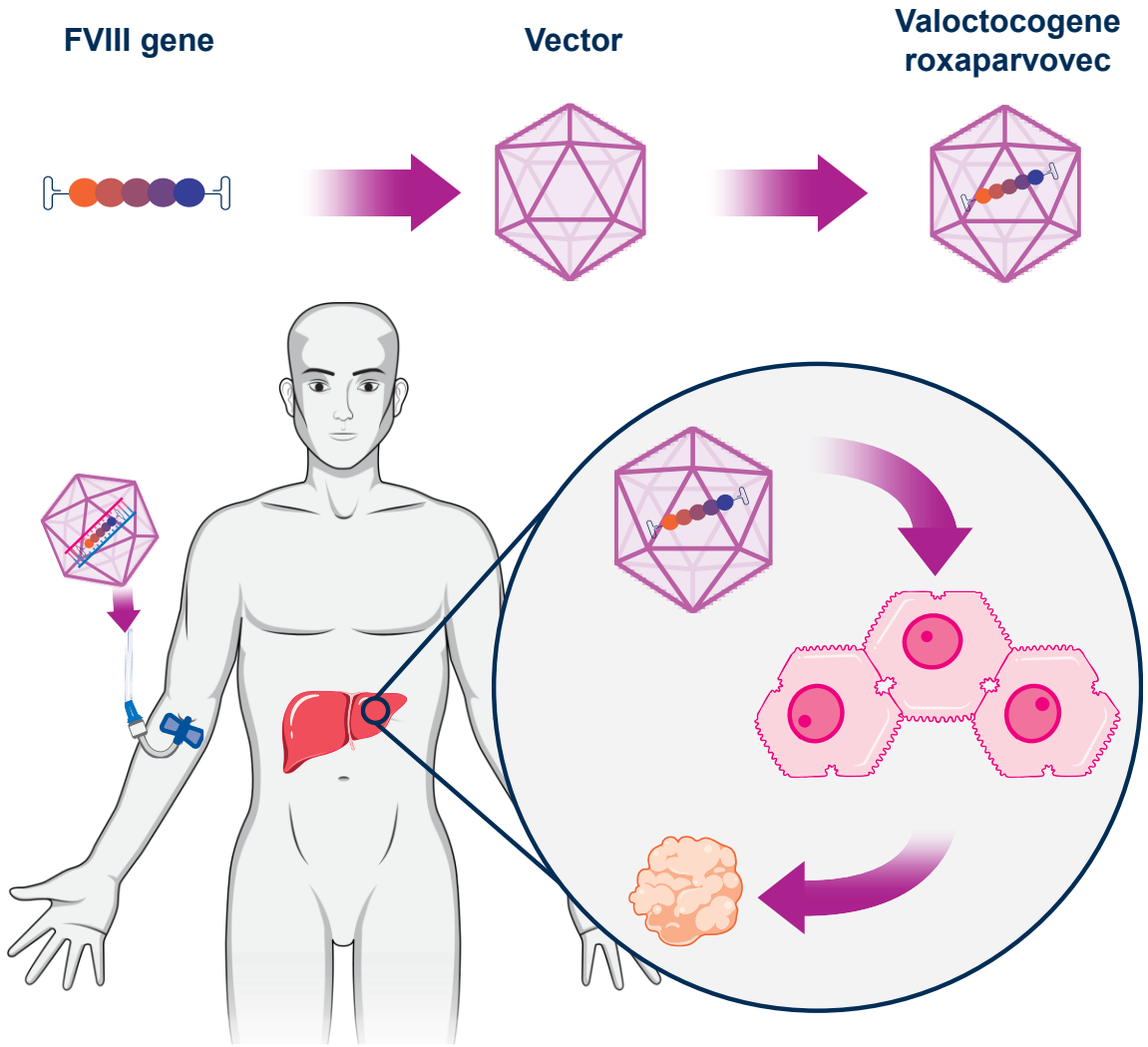
I am an employee and stockholder of BioMarin Pharmaceutical Inc.

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)[1–4]

Participants who received $6x10^{13}$ vg/kg valoctocogene roxaparvovec in the GENEr8-1 trial had improved protection from bleeds compared with regular FVIII prophylaxis over 5 years[1–5]

Individuals with active or prior FVIII inhibitors were excluded from GENEr8-1



FVIII, factor VIII.

1. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013–25. 2. Mahlangu J, et al. *N Engl J Med*. 2023;388:694–705. 3. Madan B, et al. *J Thromb Haemost*. 2024;22:1880–93. 4. Leavitt A, et al. *Res Pract Thromb Haemost*. 2024;8:e102615. 5. Mahlangu J, et al. *Haemophilia*. 2025;31(suppl 2):13–14.

Preclinical studies provide strong evidence of gene therapy-mediated ITI[1–3]

Inhibitors develop in 25%–40% of individuals with HA receiving replacement therapy[1,4]

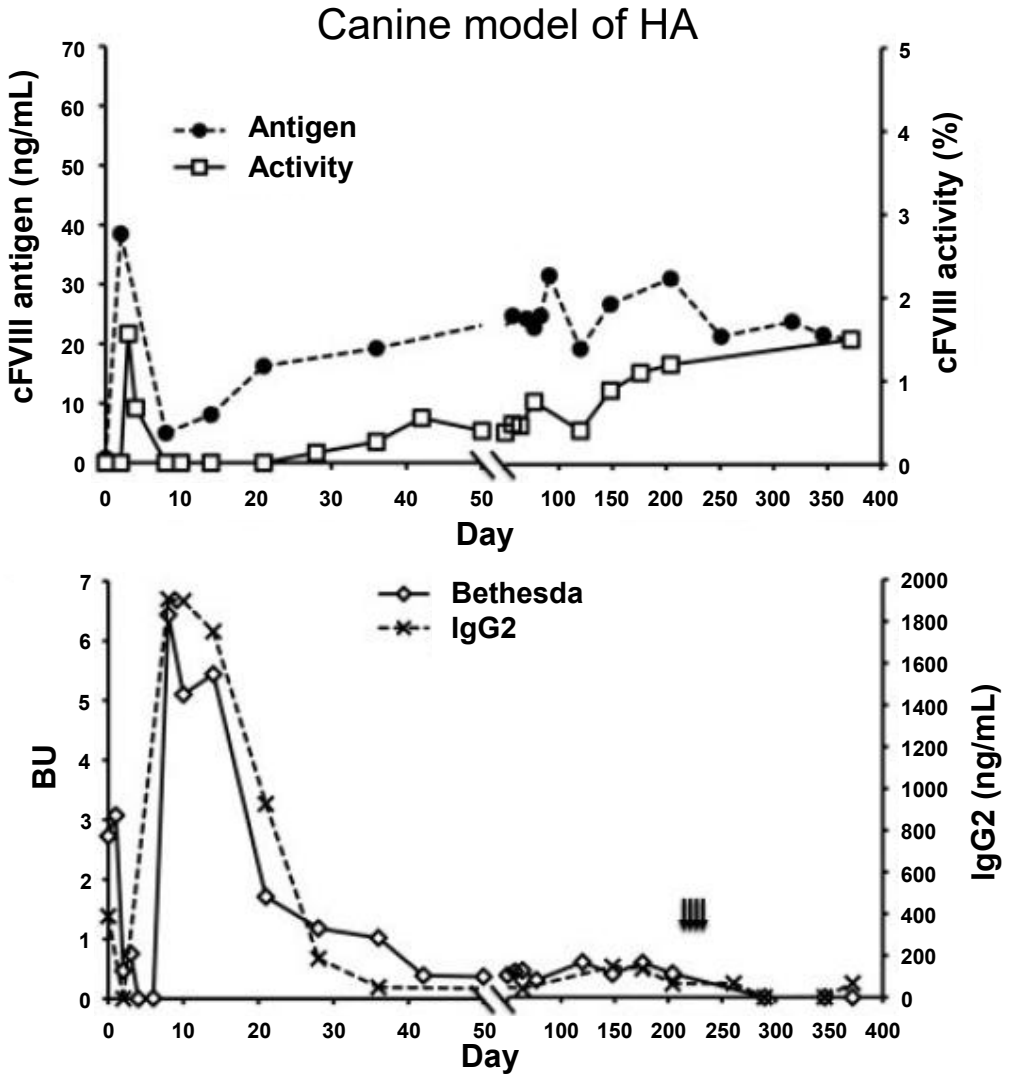


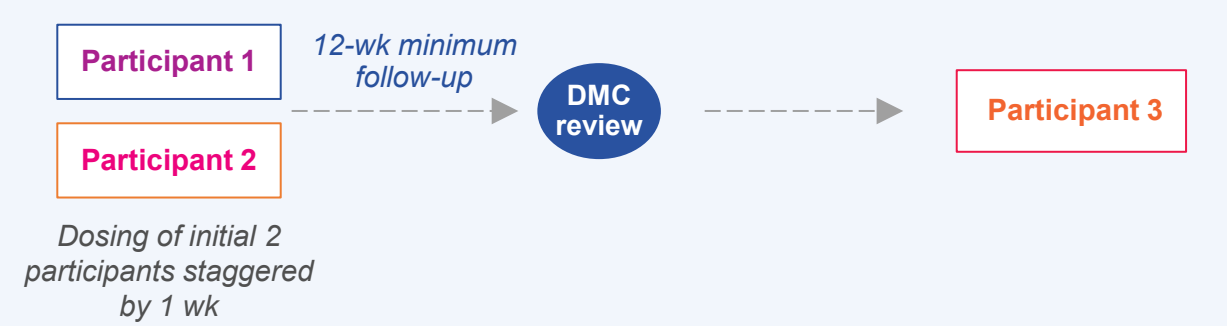
Figure adapted from Finn JD, et al. *Blood*. 2010;116(26):5842–8.
Black arrows denote 4 weekly challenges with 500 units of rBDD-cFVIII.
BU, Bethesda units; cFVIII, canine factor VIII; HA, hemophilia A; IgG2, immunoglobulin G2; ITI, immune tolerance induction; rBDD-cFVIII, recombinant, B-domain-deleted cFVIII.

1. Merlin S, et al. *Front Immunol*. 2020;11:476. 2. Arruda VR, et al. *J Thromb Haemost*. 2016;14(6):1121–34. 3. Finn JD, et al. *Blood*. 2010;116(26):5842–8. 4. Carcao M, et al. *Haemophilia*. 2019;25(4):676–84.

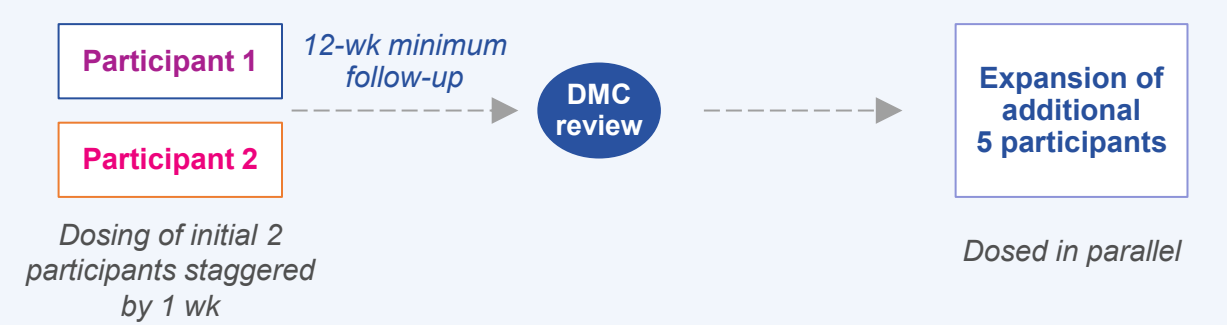
GENEr8-INH study design

Primary objective: *To assess the safety of a single IV administration of valoctocogene roxaparvovec for individuals with severe HA and active (part A) or prior (part B) FVIII inhibitors*

Part A: Active inhibitor population (n = 3)



Part B: Prior inhibitor population (n = 7)



- **Primary outcome**:
  - Safety
- **Secondary outcomes**:
  - FVIII activity and inhibitor titer
  - Annualized bleeding rate
  - Use of hemophilia therapy

DMC, data monitoring committee; FVIII, factor VIII; HA, hemophilia A; IV, intravenous; wk, week.

Participant demographics

Participants completed between 44.7 and 122.7 weeks of follow-up and all remained on study

	Part A (n = 3)	Part B (n = 7)	Parts A and B combined (N = 10)
Age, years, mean (SD)	25.3 (5.7)	32.0 (12.7)	30.0 (11.2)
Age at enrollment, n (%)			
18 to <30 years	2 (66.7)	4 (57.1)	6 (60.0)
30 to <50 years	1 (33.3)	2 (28.6)	3 (30.0)
≥50 years	0	1 (14.3)	1 (10.0)
Race, n (%)			
White	2 (66.7)	2 (28.6)	4 (40.0)
Asian	1 (33.3)	4 (57.1)	5 (50.0)
Not provided	0	1 (14.3)	1 (10.0)
Male sex, n (%)	3 (100.0)	7 (100.0)	10 (100.0)
Treatment with prophylaxis, n (%)	3 (100.0)	7 (100.0)	10 (100.0)
FVIII utilization (IU/kg/year), mean (SD)	NA	4883.3 (1524.7)	NA
FVIII infusion rate (infusions/year), mean (SD)	NA	105.3 (40.6)	NA
ABR (treated bleeds/year), mean (SD)	0.9 (1.6)	5.5 (7.4)	4.1 (6.5)
Medical history, n (%)			
Hepatitis B	0	1 (14.3)	1 (10.0)
Hepatitis C	0	2 (28.6)	2 (20.0)
HIV	0	0	0
Liver disease	0	2 (28.6)	2 (20.0)

ABR, annualized treated bleeding rate; HIV, human immunodeficiency virus; NA, not applicable; SD, standard deviation.

Safety signals are consistent with results from GENEr8-1

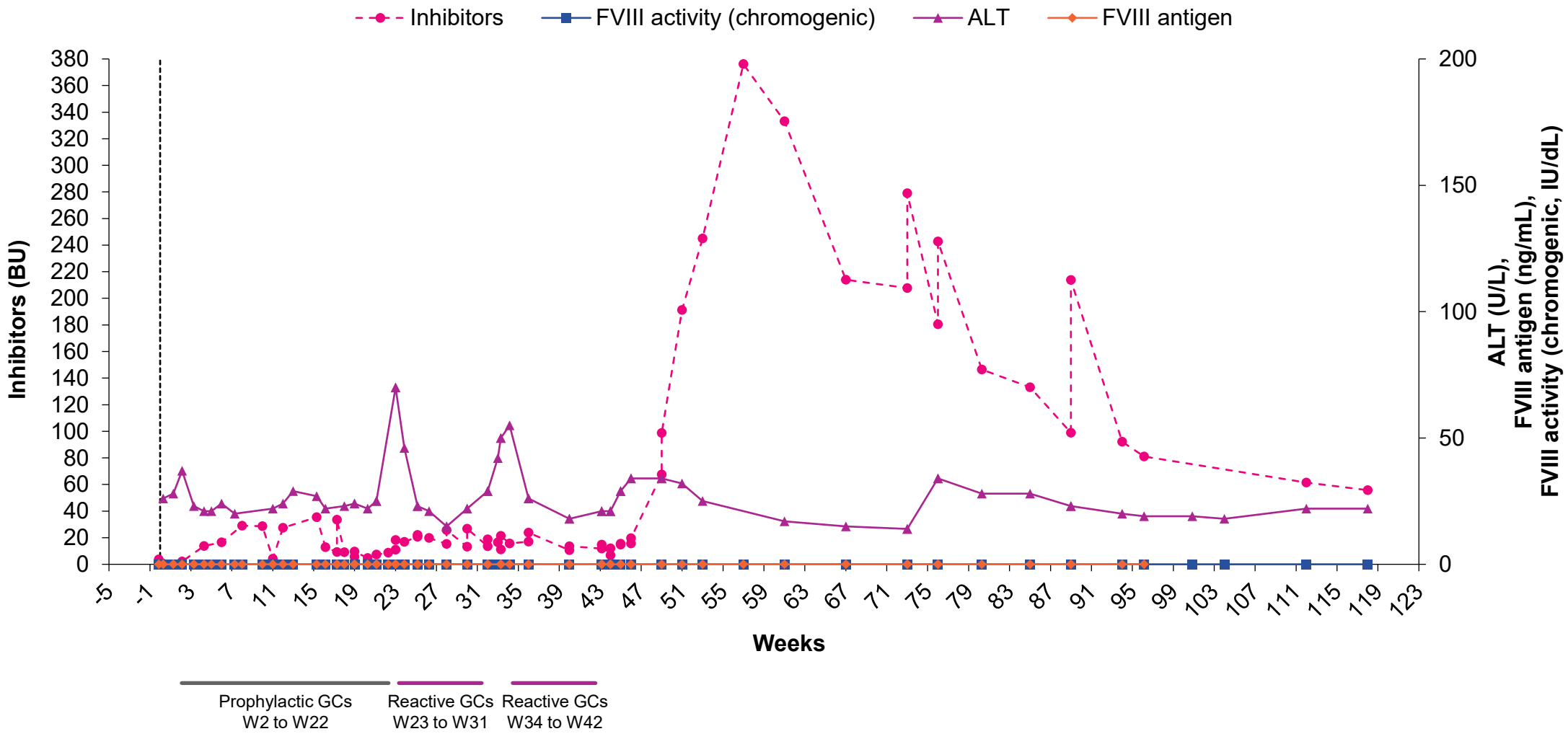
Part A and B combined safety outcomes

Safety outcomes	Part A participants (n = 3)	Part B participants (n = 7)	Combined (N = 10)
AEs, n (%)	3 (100.0)	7 (100.0)	10 (100.0)
SAEs, n (%)	0	1 (14.3)	1 (10.0)
Treatment-related AEs, n (%)	2 (66.7)	6 (85.7)	8 (80.0)
Treatment-related SAEs, n (%)	0	1 (14.3)	1 (10.0)
AEs grade ≥3, n (%)	1 (33.3)	2 (28.6)	3 (30.0)
ALT elevation, n (%)	2 (66.7)	7 (100.0)	9 (90.0)
Used corticosteroids for ALT elevation, n (%)	2 (66.7)	4 (57.1)	6 (60.0)
Used prophylactic corticosteroids, n (%)	2 (66.7)	2 (28.6)	4 (40.0)
FVIII inhibitor recurrence, n (%)	NA	0	0

AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; NA, not applicable; SAE, serious AE.

Part A: Active inhibitors

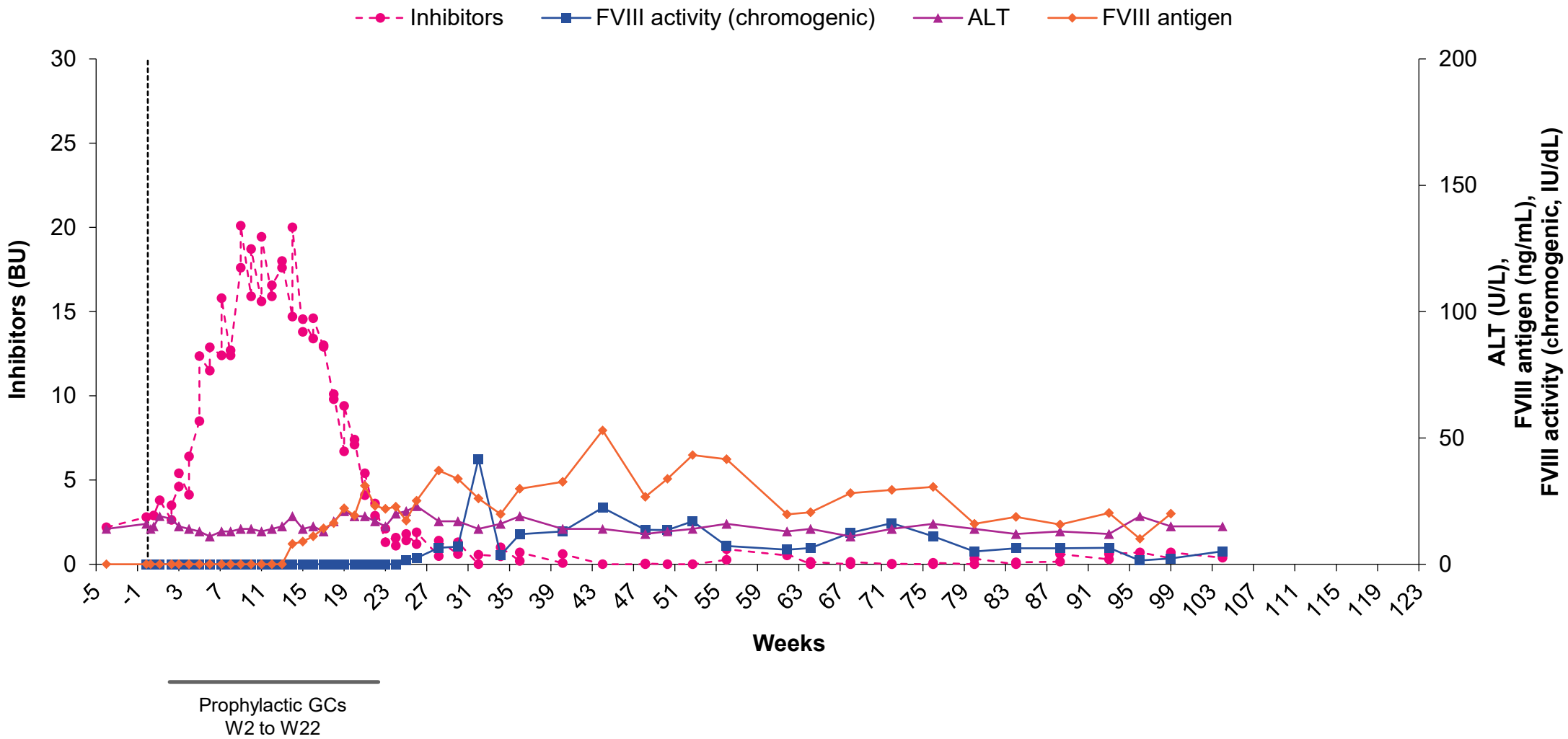
30-year-old male receiving emicizumab



ALT normal range, 5–48 U/L. FVIII activity was assessed by chromogenic assay: values <1.5 IU/dL were imputed as 0; FVIII antigen values <4.7 ng/mL were imputed as 1.
ALT, alanine aminotransferase; BU, Bethesda units; GC, glucocorticoid; FVIII, factor VIII; W, week.

Part A: Active inhibitors

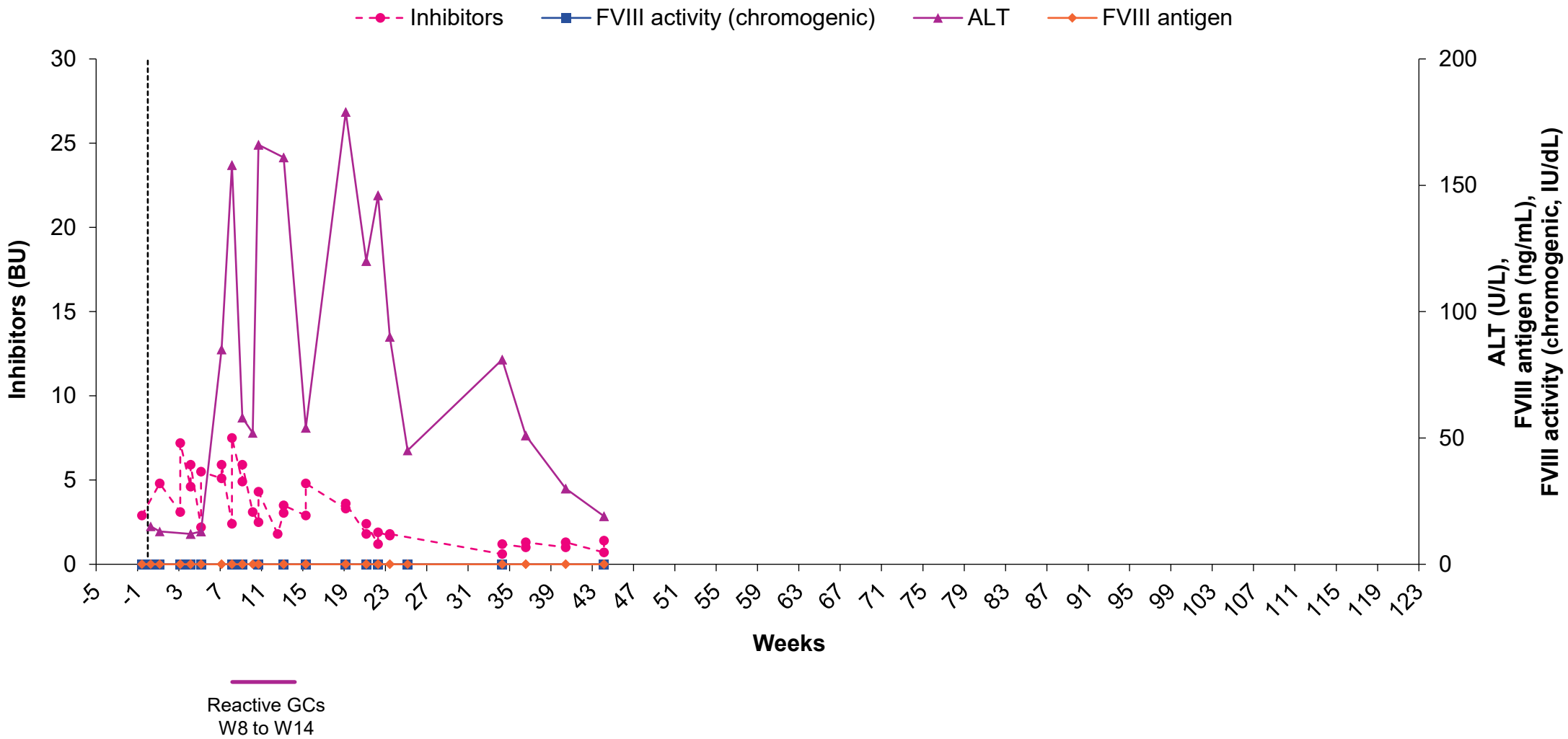
27-year-old male receiving emicizumab



ALT normal range, 5–48 U/L. FVIII activity was assessed by chromogenic assay: values <1.5 IU/dL were imputed as 0; FVIII antigen values <4.7 ng/mL were imputed as 1.
ALT, alanine aminotransferase; BU, Bethesda units; GC, glucocorticoid; FVIII, factor VIII; W, week.

Part A: Active inhibitors

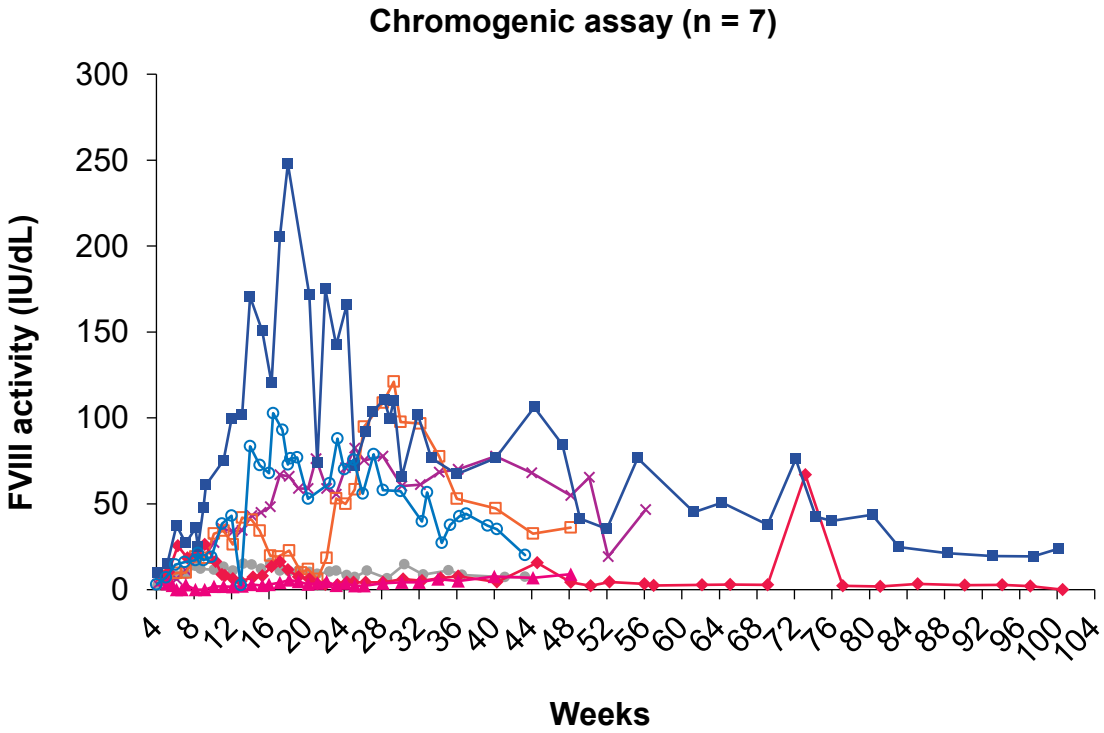
19-year-old male receiving anti-inhibitor coagulant complex

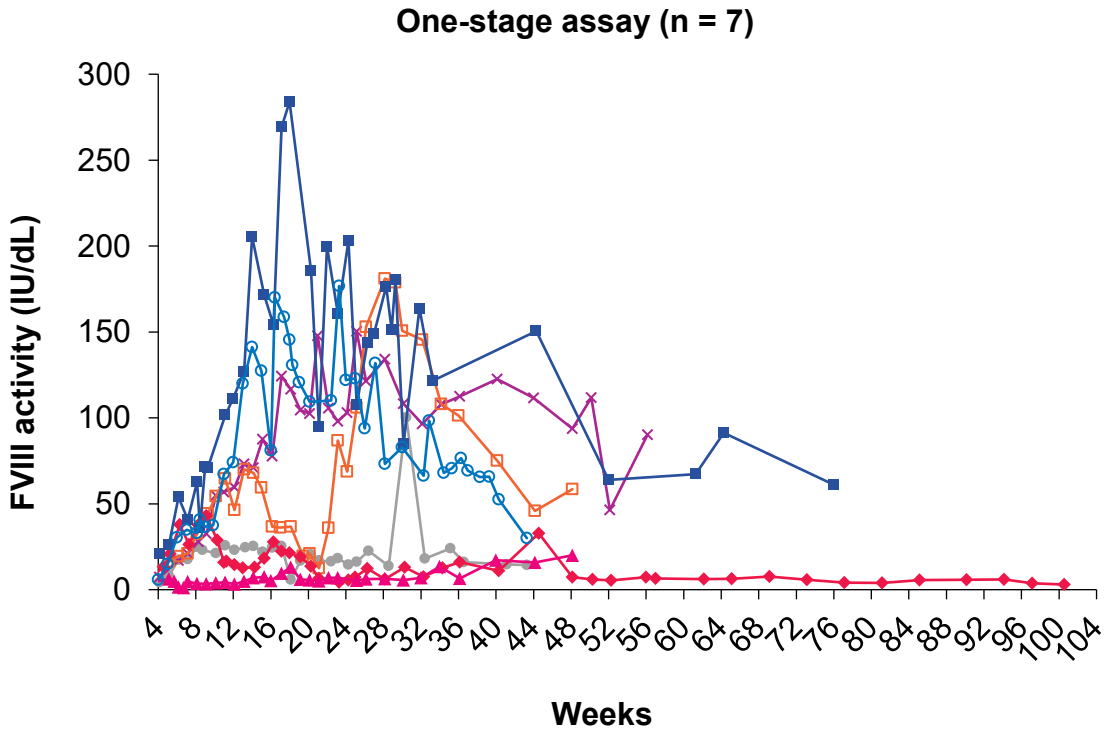


ALT normal range, 5–48 U/L. FVIII activity was assessed by chromogenic assay: values <1.5 IU/dL were imputed as 0; FVIII antigen values <4.7 ng/mL were imputed as 1.
ALT, alanine aminotransferase; BU, Bethesda units; GC, glucocorticoid; FVIII, factor VIII; W, week.

Part B: Prior inhibitors

Efficacy outcomes in participants with prior inhibitors are consistent with the results of GENEr8-1





FVIII activity values <1.5 IU/dL were imputed as 0.
FVIII, factor VIII.

Part B: Prior inhibitors

Efficacy outcomes in participants with prior inhibitors are consistent with the results of GENEr8-1

Efficacy outcomes	Weeks 25–28	GENEr8-1 trial Week 26	Weeks 49–52	GENEr8-1 trial Weeks 49–52
n	7	112	5	112
FVIII activity, IU/dL, mean (SD)				
Chromogenic assay	50.1 (43.8)	n = 132 53.4 (SE, 4.8)	25.8 (18.2)	n = 132 42.8 (SE, 4.0)
ABR, bleeds/year	0	Mean, 1.1	0	Mean, 0.9
Participants with zero treated bleeds, n (%)	7 (100.0)	94 (83.9)	7 (100.0)	92 (82.1)
AFR, infusions/year	0	Mean, 1.6	0	Mean, 1.5
Participants with zero FVIII infusions, n (%)	7 (100.0)	89 (79.5)	7 (100.0)	85 (75.9)

ABR, annualized bleeding rate; AFR, annualized FVIII infusion rate; FVIII, factor VIII; SD, standard deviation; SE, standard error.

Conclusions

Valoctocogene roxaparvovec safety was similar for participants with or without inhibitors and had promising efficacy

- Participants showed a similar safety profile to the GENEr8-1 trial regardless of inhibitor status
- Prior inhibitor status was not associated with a relapse of inhibitors
- All 3 active inhibitor participants had increased FVIII inhibitor titers, suggesting that FVIII is being produced. FVIII activity was detectable in 1 participant
- Prior inhibitor participants had kinetics of FVIII activity similar to the GENEr8-1 trial
- Prior inhibitor participants had no bleeds and no FVIII infusions

FVIII, factor VIII.

Acknowledgments

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