European Association for Haemophilia and Allied Disorders (EAHAD) 2024

SLAM session 6

Safety and efficacy of valoctocogene roxaparvovec with prophylactic corticosteroids: 1-year GENEr8-3 results

Margareth C Ozelo[1], Jane Mason[2,3], Amy L Dunn[4], Paula Ribeiro Villaça[5], Ming-Ching Shen[6], Suresh K Agarwal[7], Urooj Imtiaz[7], Hai Liu[7], Tara M Robinson[7]

[1]Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, SP, Brazil; [2]Queensland Haemophilia Centre, Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [3]University of Queensland, Brisbane, QLD, Australia; [4]The Division of Hematology, Oncology, and BMT at Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, OH, USA; [5]Hospital das Clínicas da Universidade de São Paulo, SP, Brazil; [6]Division of Hematology/Oncology, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan; [7]BioMarin Pharmaceutical Inc., Novato, CA, USA

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Disclosures

I have the following potential conflicts of interest to report:

- **Research support**: Bayer, BioMarin Pharmaceutical Inc., Pfizer, Roche, Sanofi, and Takeda
- **Participated in advisory boards:** Bayer, BioMarin Pharmaceutical Inc., Pfizer, Sanofi, and Takeda
- **Receipt of honoraria or consultation fees:** BioMarin Pharmaceutical Inc., Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda

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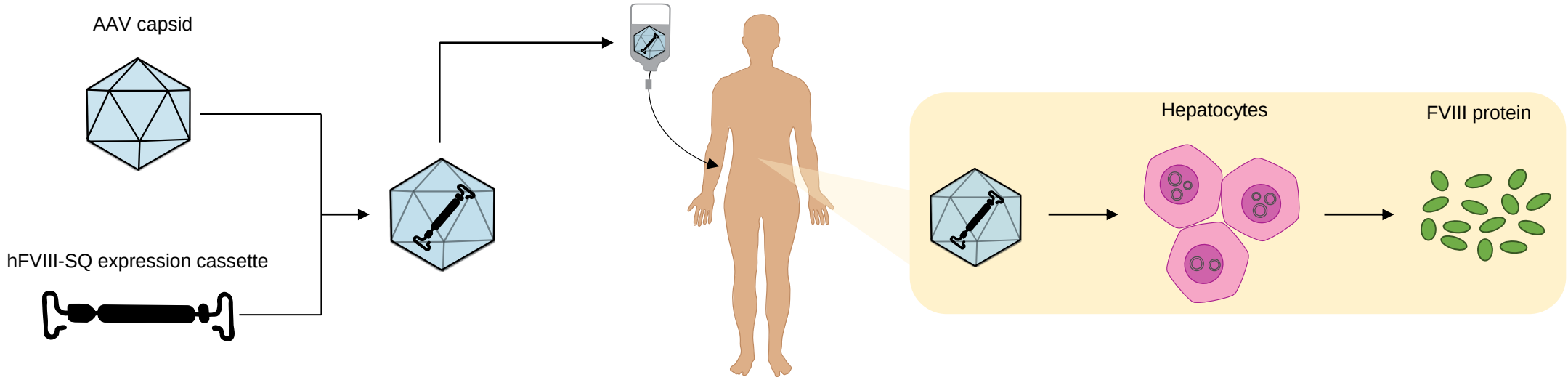
Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a B-domain-deleted FVIII coding sequence that enables endogenous FVIII production in people with severe HA (FVIII ≤1 IU/dL)[1,2]
- Prophylactic CS regimens are hypothesized to mitigate cellular immune responses that may lead to transaminase elevation and loss of transgene-derived protein[3-6]
- GENEr8-3 is a single-arm, open-label, phase 3b trial evaluating the efficacy and safety of valoctocogene roxaparvovec with a concomitant prophylactic CS regimen for people with severe HA



AAV5, adeno-associated virus serotype 5; CS, corticosteroid; FVIII, factor VIII; HA, hemophilia A; hFVIII-SQ, human FVIII, SQ variant.

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(8):694-705. 3. Nathwani AC, et al. *N Engl J Med*. 2014;371:1994-2004. 4. Nathwani AC, et al. *N Engl J Med*. 2011;365:2357-65. 5. Manno CS, et al. *Nat Med*. 2006;12:342-7. 6. Handyside, et al. *Hum Gene Ther*. 2024;35:36-47.

GENEr8-3 study design

Eligible participants

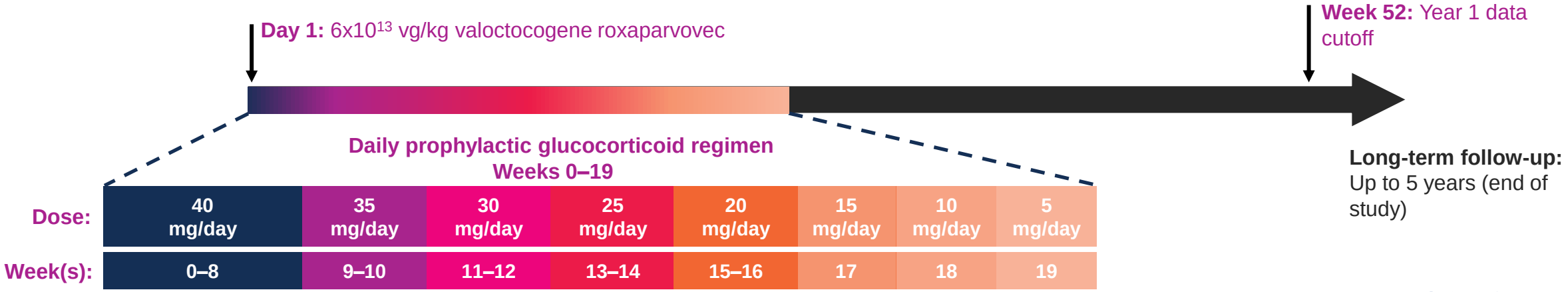
- Adult men with severe HA (FVIII ≤1 IU/dL)
- On HA prophylaxis for ≥12 months
- No history of FVIII inhibitors
- Anti-AAV5 antibodies <MRD were allowed for ≤25% of participants
  - No participants with detectable anti-AAV5 antibody titers enrolled
- ≥12 months of historical bleeds and hemophilia therapy records
- No significant liver dysfunction

Endpoints

- Safety
- FVIII activity
- Annualized bleeding rate (treated and all bleeds)
- Annualized FVIII utilization rate
- HRQOL

Efficacy evaluation period

- Began 5 weeks post-valoctocogene roxaparvovec infusion, or post-cessation of FVIII prophylaxis plus the FVIII product washout period, and ended at the last study visit up to the 1-year data cutoff



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; HA, hemophilia A; HRQOL, health-related quality of life; MRD, minimum required dilution.

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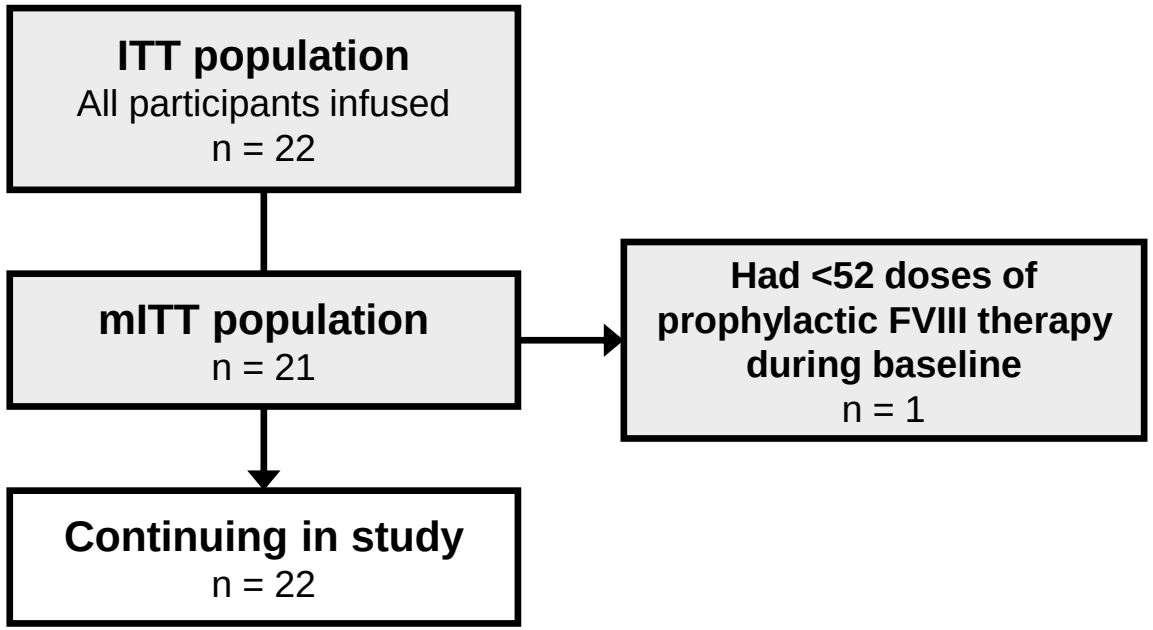
Participant demographics, characteristics, and disposition

Study populations

- Safety analyses were based on the ITT population
- Efficacy analyses were based on the mITT population
- As of the 1-year data cutoff, all participants are continuing in the study



	mITT (n = 21)	ITT (n = 22)
Age (years), mean ± SD	28.4 ± 7.4	28.0 ± 7.4
Race, n (%)		
Asian	1 (4.8)	2 (9.1)
Black	2 (9.5)	2 (9.1)
White	18 (85.7)	18 (81.8)
Ethnicity, n (%)		
Hispanic or Latino	1 (4.8)	1 (4.5)
History of hepatitis B, n (%)	0 (0.0)	0 (0.0)
History of hepatitis C, n (%)	3 (14.3)	3 (13.6)
History of HIV, n (%)	0 (0.0)	0 (0.0)
History of hepatic steatosis, n (%)	1 (4.8)	1 (4.5)
Number of problem joints, n (%)[a]		
0	15 (71.4)	16 (72.7)
1	3 (14.3)	3 (13.6)
2	2 (9.5)	2 (9.1)
3	1 (4.8)	1 (4.5)

[a]Problem joints were identified by the investigators at baseline and were defined as joints with any of the following symptoms: chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.

FVIII, factor VIII; HA, hemophilia A; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified ITT; SD, standard deviation.

Safety assessment in year 1

- In year 1, all participants experienced an AE
  - 90.9% of participants experienced a treatment-related AE as determined by the investigator
  - 31.8% of participants experienced an AE grade ≥3
- One participant experienced a treatment-unrelated SAE
- No participants developed thromboembolic events, inhibitors, or malignancies
- The most common AE was ALT elevation

Participants, n (%)	ITT (N = 22)
AEs	22 (100.0)
SAEs	1 (4.5)
Treatment-related AE	20 (90.9)
Treatment-related SAE	0 (0.0)
Any AE of grade ≥3	7 (31.8)
Deaths	0 (0.0)
Any AE related to immunosuppressant use	19 (86.4)
AEs related to glucocorticoid use	19 (86.4)
AEs related to non-steroidal immunosuppressant use	0 (0.0)
AEs of special interest	
ALT elevation[a]	20 (90.9)
Potential Hy's law cases	0 (0.0)
Infusion-related reactions[b]	5 (22.7)
Infusion-associated reactions[c]	12 (54.5)
Systemic hypersensitivity	3 (13.6)
Anaphylactic or anaphylactoid reactions	0 (0.0)
Thromboembolic events	0 (0.0)
FVIII inhibitors	0 (0.0)
Malignancy (excluding NMSC)	0 (0.0)

[a]ALT elevation was defined as ALT >ULN (43 U/L) or ≥1.5x baseline. [b]Infusion-related reactions were AEs that occurred during or within 6 hours of valoctocogene roxaparvovec infusion.
[c]Infusion-associated reactions were AEs that occurred within 48 hours of valoctocogene roxaparvovec infusion.
AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; ITT, intention-to-treat; NMSC, non-melanoma skin cancer; SAE, serious adverse event; ULN, upper limit of normal.

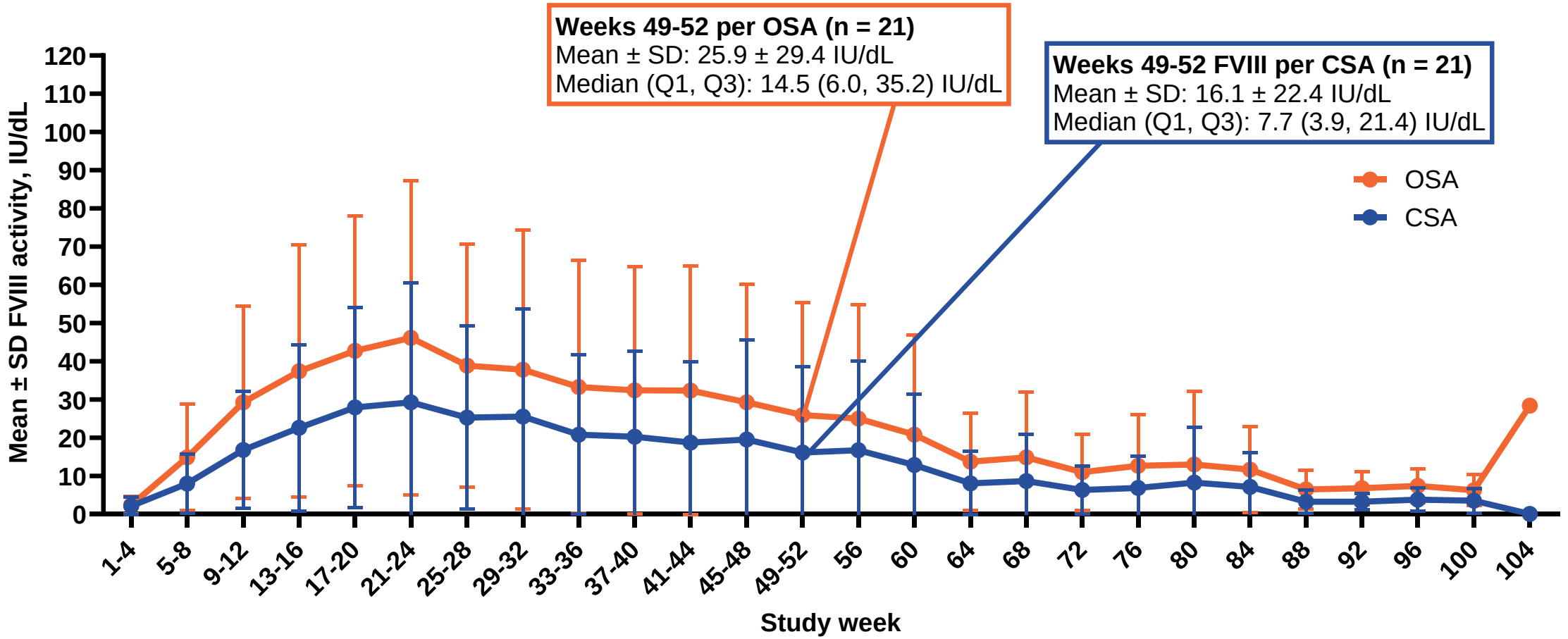
ALT elevations

- In year 1, 90.9% of participants experienced an ALT elevation (>ULN or ≥1.5x baseline ALT)
- Prophylactic CS had no clear benefit on ALT elevations
  - Mean peak ALT elevation above the ULN was higher in GENEr8-3 compared with GENEr8-1
  - The proportion of participants with ALT >ULN was lower in GENEr8-3 compared with GENEr8-1

Participants, n (%)	GENEr8-3 ITT (N = 22)	GENEr8-1 ITT (N = 134)
Participants with ALT >ULN, n (%)	10 (45.5)	106 (79.1)
Mean time from infusion to first episode, weeks	12.6	13.7
Mean peak ALT >ULN, U/L	192.0	114.5
Mean time from infusion to peak ALT >ULN, weeks	19.2	25.6
Participants with ALT ≥1.5x baseline, n (%)	16 (72.7)	122 (91.0)
Mean time from infusion to first episode, weeks	13.3	10.0
Participants with ALT >ULN or ALT ≥1.5x baseline, n (%)	17 (77.3)	125 (93.3)
Mean time from infusion to first episode, weeks	11.6	8.8
Total duration of episodes per participant, weeks	25.1	35.3

ALT, alanine aminotransferase; CS, corticosteroids; ITT, intention-to-treat; ULN, upper limit of normal.

FVIII activity in the mITT population



FVIII activity was imputed as 1 IU/dL at baseline, 0 IU/dL if the participant discontinued the study or if FVIII activity was below the lower limit of quantification.

CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intention-to-treat; OSA, one-stage assay; Q, quartile; SD, standard deviation.

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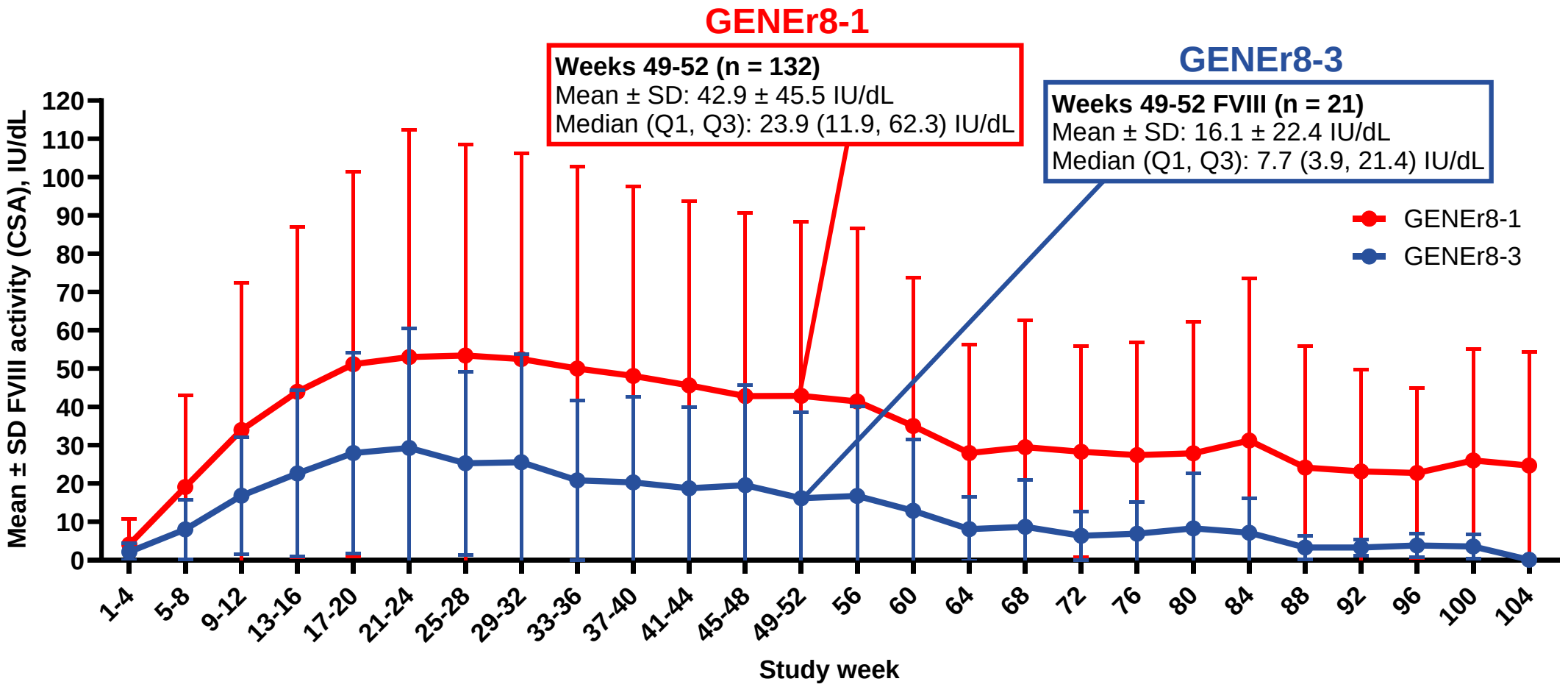
FVIII activity is lower with prophylactic CS compared with reactive CS



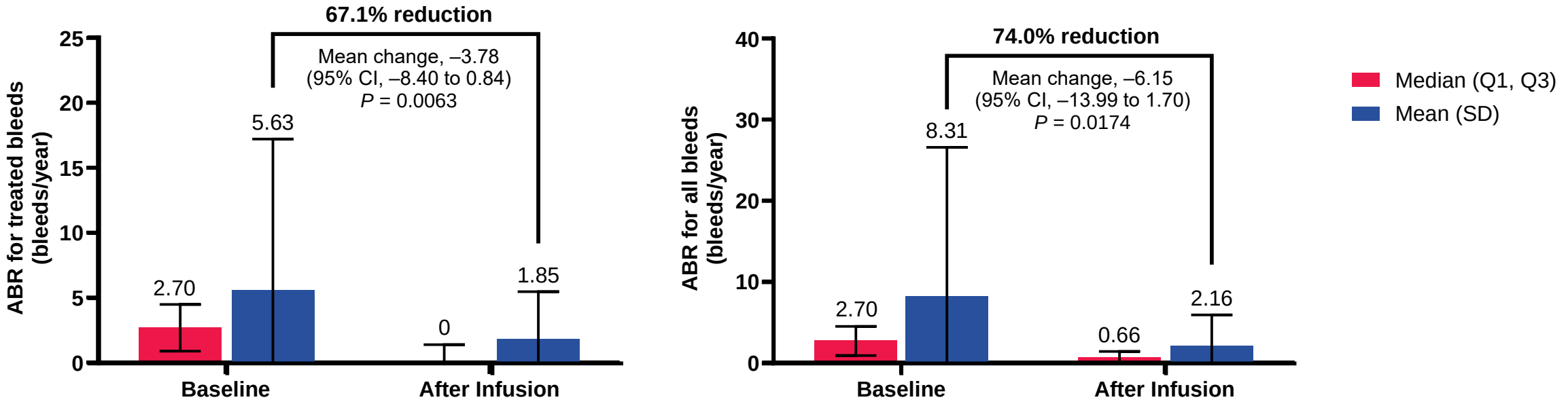
GENEr8-1, n =	132	132	132	132	132	132	132	132	132	132	132	132	132	116	84	57	51	44	36	30	29	24	21	21	19	17
GENEr8-3, n =	21	21	21	21	21	21	21	21	21	21	21	21	21	20	19	18	18	18	18	15	12	5	5	4	4	1

FVIII activity was imputed as 1 IU/dL at baseline, 0 IU/dL if the participant discontinued the study or if FVIII activity was below the lower limit of quantification.

CSA, chromogenic substrate assay; CS, corticosteroids; FVIII, factor VIII; Q, quartile; SD, standard deviation.

Reduced ABR for treated and all bleeds compared with baseline

- In the mITT population, ABRs for treated bleeds and all bleeds were lower during the efficacy evaluation period than at baseline



ABR, annualized bleed rate; CI, confidence interval; mITT, modified intention-to-treat; Q, quartile; SD, standard deviation.

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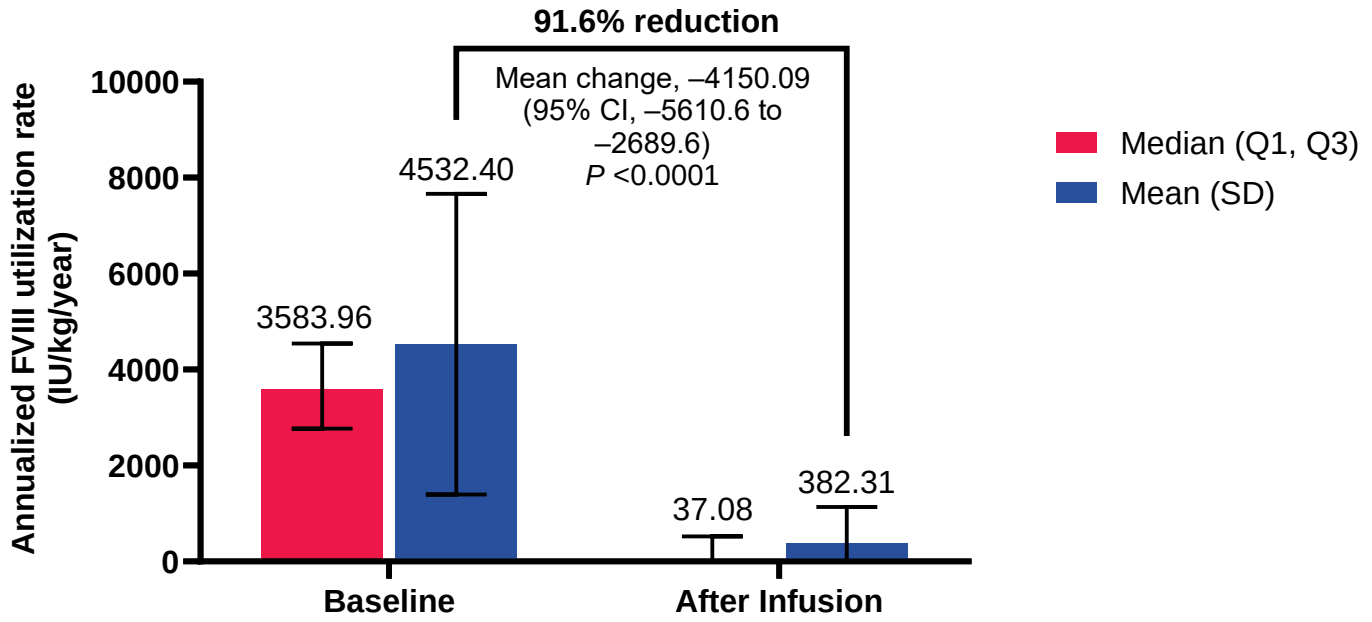
Reduced FVIII utilization compared with baseline

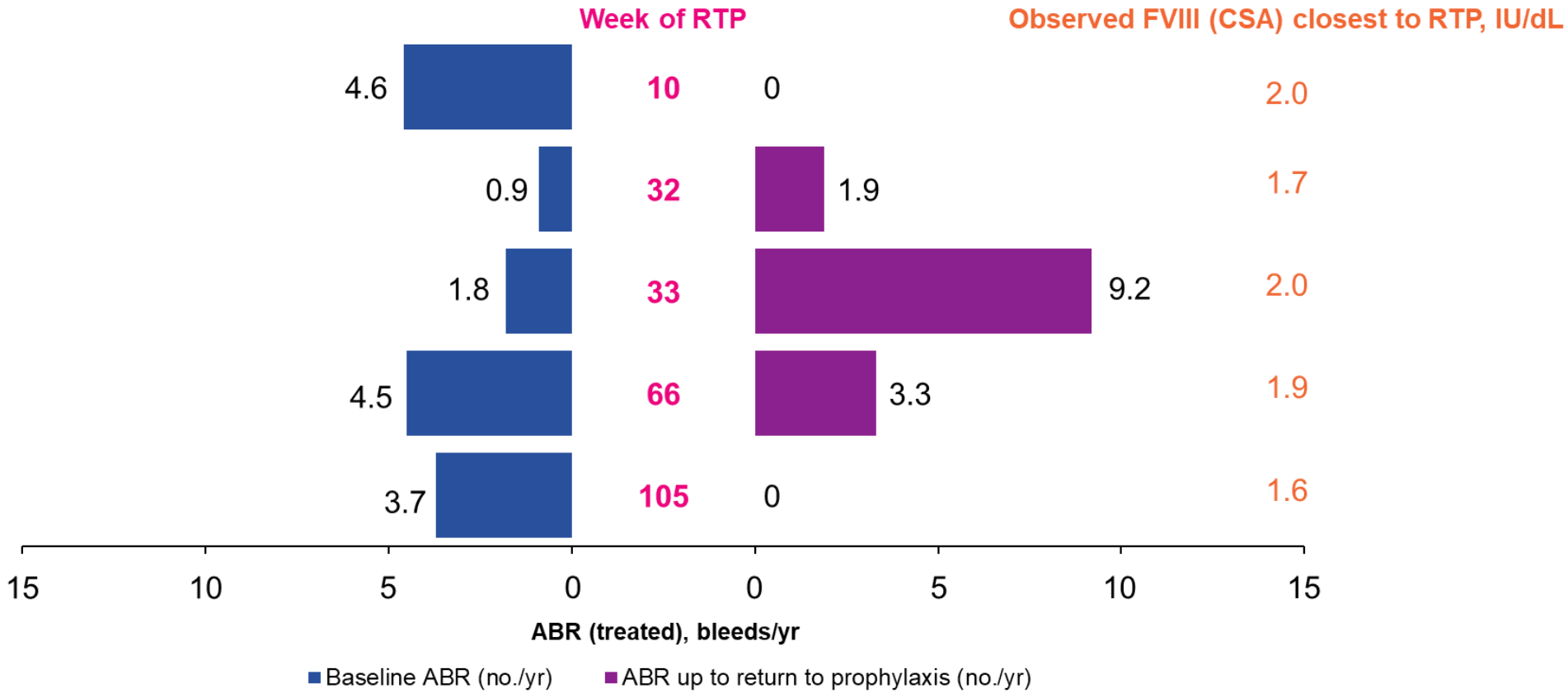
- In the mITT population, the FVIII infusion rate was lower during the efficacy evaluation period than at baseline



CI, confidence interval; FVIII, factor VIII; mITT, modified intent-to-treat; Q, quartile; SD, standard deviation.

Participants who returned to HA prophylaxis

- To date, 5 participants returned to HA prophylaxis
  - Of these 5 participants, 2 had higher ABR for treated bleeds in the efficacy evaluation period up to resumption of HA prophylaxis than during baseline

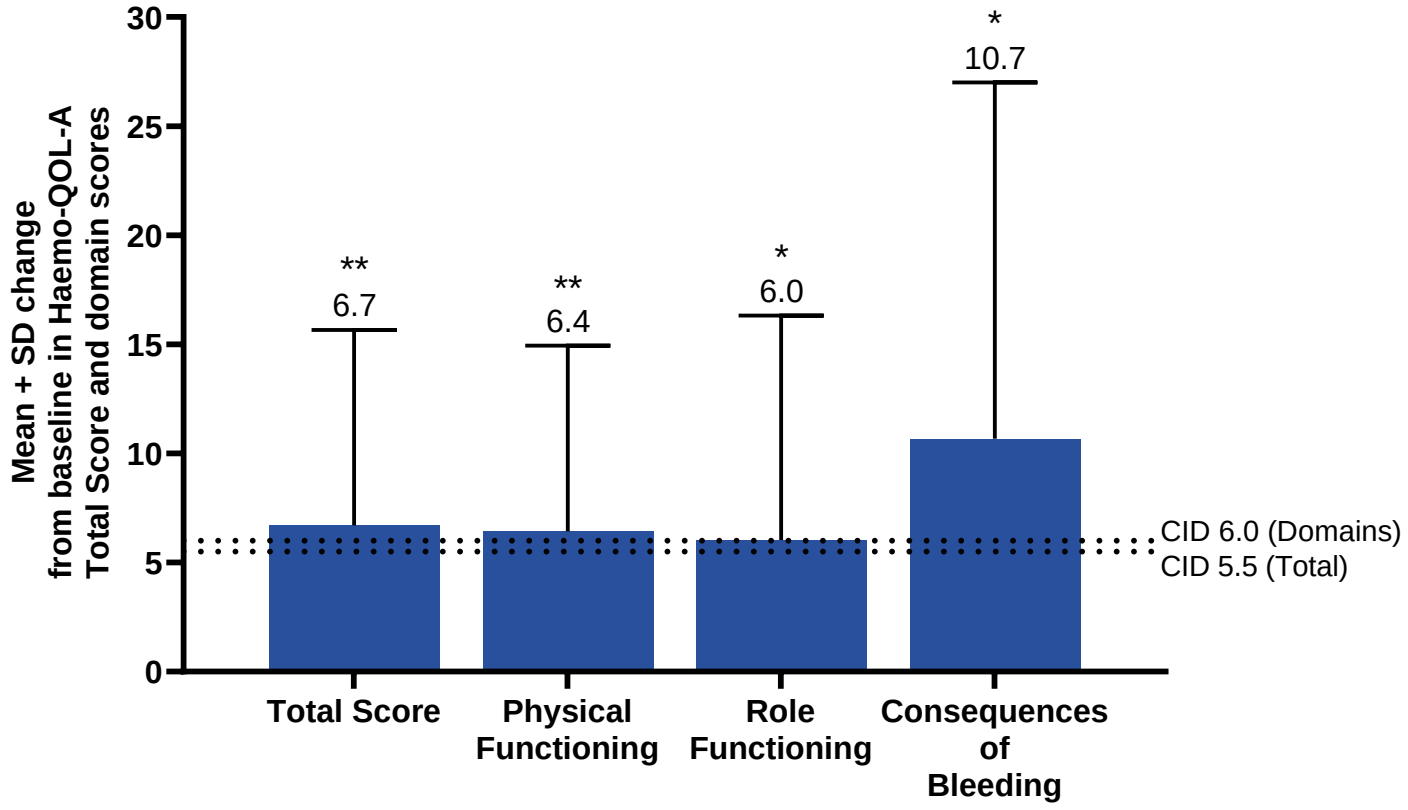


Return to prophylaxis was defined as 1 day before the first infusion of "usual FVIII prophylaxis" administered once per week for ≥4 consecutive weeks or ≥2 emicizumab injections administered within 31 days.

ABR, annualized bleeding rate; CSA, chromogenic substrate assay; FVIII, factor VIII; HA, hemophilia A; RTP, return to prophylaxis.

Improved Haemo-QOL-A at the end of year 1

- Mean change from baseline Haemo-QOL-A Total Score was 6.7 at week 52
  - This exceeds the anchor-based CID of 5.5[1]



*P <0.05. **P <0.01.
CID, clinically important difference; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; SD, standard deviation.
1. Quinn J, et al. *Patient Relat Outcome Meas*. 2022;13:169-80.

Conclusions

- Compared with year 1 FVIII activity in GENEr8-1, year 1 FVIII activity was lower with concomitant prophylactic CS in GENEr8-3
  - Mean FVIII activity: 16.1 IU/dL (GENEr8-3) vs 42.9 IU/dL (GENEr8-1)[1]
- Bleeding rates and FVIII use were significantly reduced after valoctocogene roxaparvovec infusion compared with baseline
  - Hemostatic efficacy of valoctocogene roxaparvovec was lower in GENEr8-3 than GENEr8-1, which used a reactive CS regimen[1]
  - Percent reduction in ABR for treated bleeds: 67.1% (GENEr8-3) vs 83.8% (GENEr8-1)
  - A simulation study performed by BioMarin using GENEr8-1 FVIII activity data and the GENEr8-3 sample size indicated that differences were unlikely to be caused by interindividual variability
- Internal review determined similar potency between valoctocogene roxaparvovec lots used in GENEr8-1 and GENEr8-3
- HRQOL as measured by Haemo-QOL-A was significantly improved at the end of year 1 compared with baseline
- Overall safety was similar to that observed with reactive CS use
- Assessment of valoctocogene roxaparvovec efficacy and safety with concomitant prophylactic CS in GENEr8-3 is ongoing

1.Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25

ABR, annualized bleed rate; CS, corticosteroids; FVIII, factor VIII; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; HRQOL, health-related quality of life.

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