Endogenous FVIII activity and procedure-related FVIII use and bleeding:
Post hoc analysis of GENEr8-1

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Disclosures for Doris V Quon

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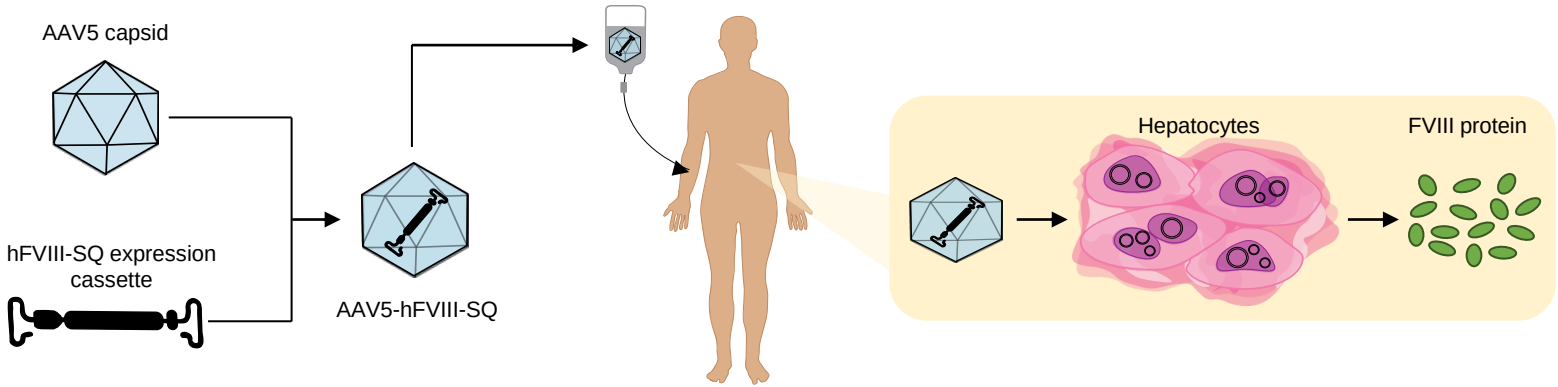
Evaluating endogenous FVIII activity and procedure-related FVIII use following 2 years of treatment with valoctocogene roxaparvovec

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence to hepatocytes using a recombinant AAV5 vector, enabling endogenous FVIII production in people with severe haemophilia A[1-4]
- In GENEr8-1, an open-label, phase 3 trial, participants achieved FVIII activity providing improved protection from bleeding compared with prophylaxis for 52 and 104 weeks[4,5]
- Here, we present findings from a post hoc analysis of procedures in GENEr8-1 after 2 years of follow-up, with a focus on FVIII use, bleeding outcomes, and rationale for PI decisions



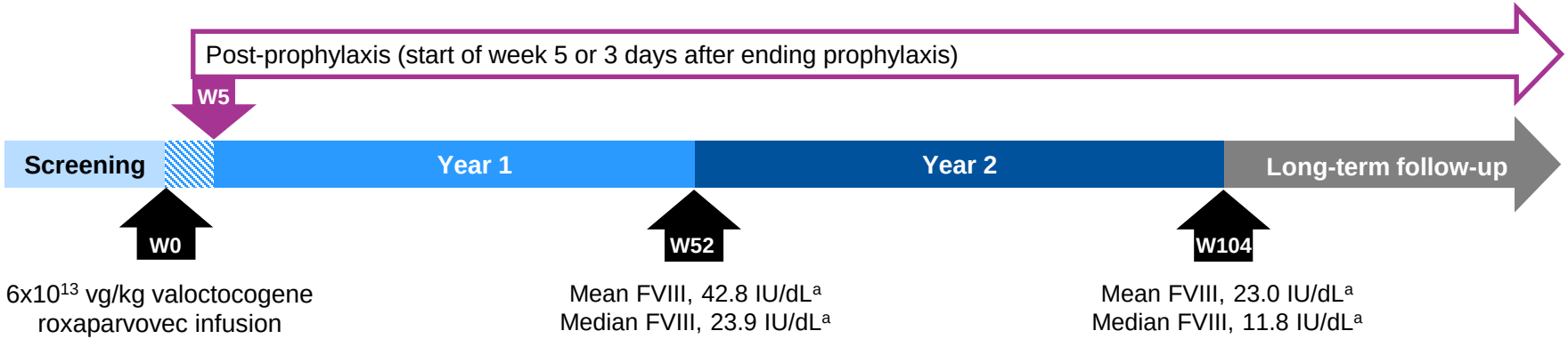
AAV, adeno-associated virus serotype 5; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant; PI, principal investigator.

1. Rangarajan S, et al. *N Engl J Med*. 2017;377(26):2519-30; 2. Pasi KJ, et al. *N Engl J Med.* 2020;382(1):2940; 3. Pasi KJ, et al. *Haemophilia.* 2021;27(6):947-56; 4. Ozelo M, et al. *N Engl J Med.* 2022;386(11):1013-25; 5. Mahlangu J, et al. 15th Annual Congress of EAHAD. February 2–4, 2022.

Phase 3 GENEr8-1 study design

Eligible participants

- Participants directly enrolled or were rolled over from the non-interventional study BMN 270-902
- Adult men with severe haemophilia A (FVIII ≤1 IU/dL)
- Previously receiving FVIII prophylaxis
- No history of FVIII inhibitors or anti-AAV5 antibodies



[a]FVIII activity measured by the chromogenic substrate assay.
AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; W, week.

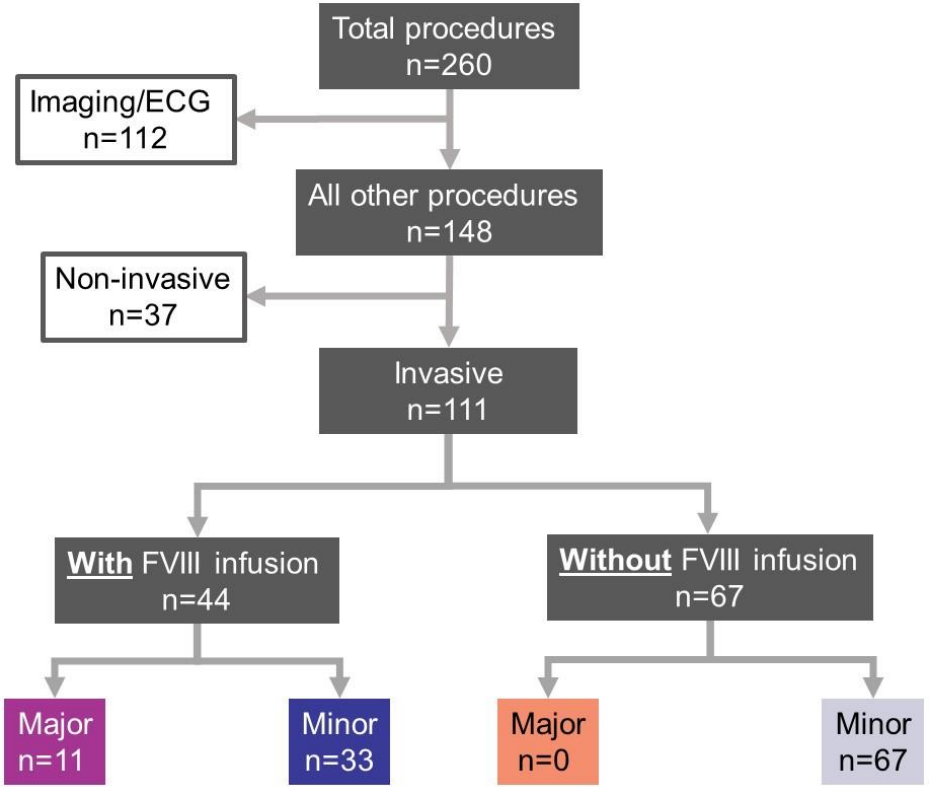
Baseline demographics and characteristics of ITT population

Baseline characteristics[1]	ITT n=134
Age, years, mean ± SD	31.7 ± 10.3
Race, n (%)	
White	96 (71.6)
Asian	19 (14.2)
Black or African American	15 (11.2)
Hawaiian or Pacific Islander	1 (0.7)
Not provided	3 (2.2)
Hispanic or Latino ethnicity, n (%)	7 (5.2)
BMI, kg/m^2, mean ± SD	25.3 ± 4.6
Medical history, n (%)	
Hepatitis B	20 (14.9)
Hepatitis C	41 (30.6)
HIV	2 (1.5)
Number of problem joints,[a] n (%)	
0	97 (72.4)
1	17 (12.7)
2	9 (6.7)
3	8 (6.0)
>3	3 (2.2)

[a]Problem joints were those with chronic joint pain, chronic synovitis, haemophilic arthropathy, limited motion, or recurrent bleeding.
BMI, body mass index; HIV, human immunodeficiency virus; ITT, intent to treat; SD, standard deviation.
1. Ozelo M, et al. *N Engl J Med.* 2022;386(11):1013-25.

Procedures performed during GENEr8-1

- In total, 77 participants underwent 260 total procedures
- Types of procedures[1]
  - Non-invasive: eg, tattoo, dental cleaning
  - Invasive:
    - Major: eg, joint debridement, arthrodesis
    - Minor: eg, dental extraction, biopsies
- PIs were sent questionnaires asking what factors influenced their decision to perform procedures without FVIII infusions



ECG, echocardiogram; FVIII, factor VIII; PI, principal investigator.

1. Solimeno LP, et al. *Clin Applied Thomb Haemost*. 2018;24[4]:549–59.

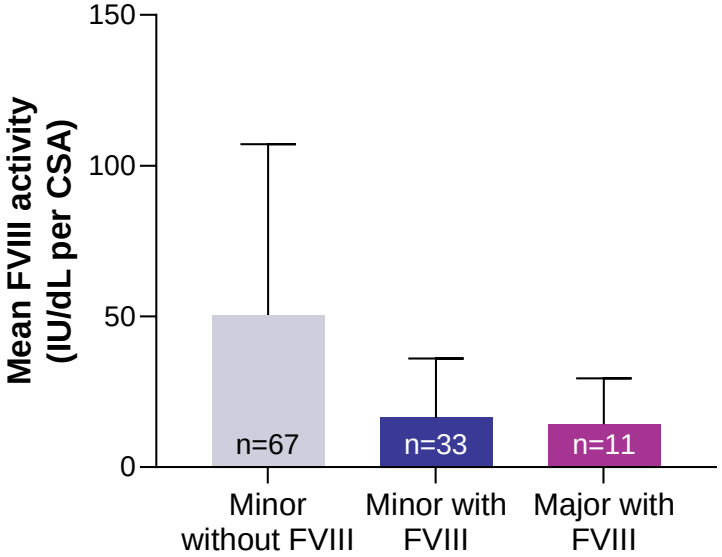
Perioperative management for participants in GENEr8-1

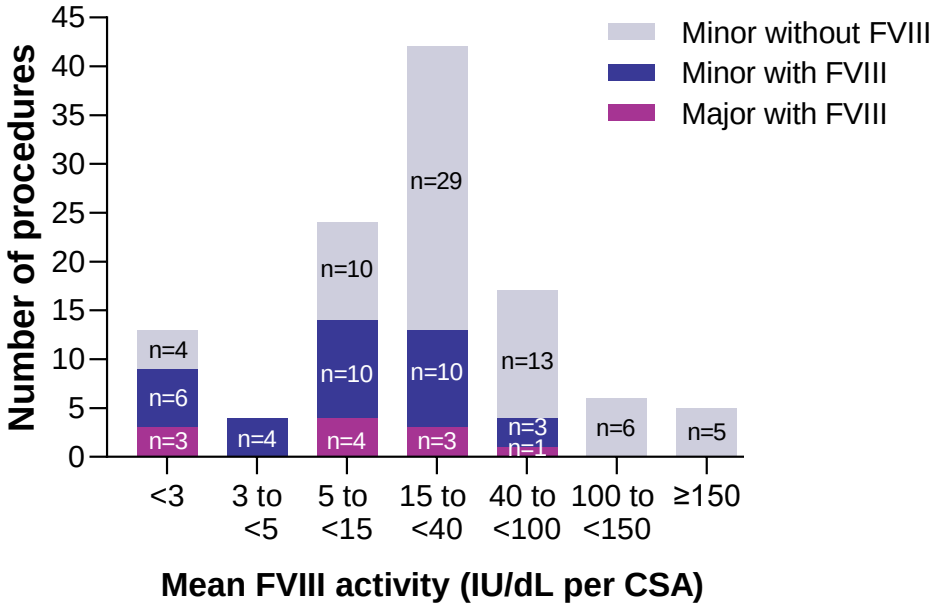
- Major invasive procedures were performed with FVIII treatment regardless of participant FVIII level
- Compared with minor procedures, major procedures were associated with a higher:
  - FVIII dose
  - Number of FVIII infusions
  - Days of post-operative FVIII treatment

	Minor invasive procedures	Major invasive procedures
Mean FVIII dose, IU/kg (min/max)	67.2 (14–324)	255.4 (103–538)
Number of FVIII infusions, n (min/max)	2.2 (1–13)	8.8 (3–21)
Days of post-operative FVIII, n (min/max)	1.8 (1–7)	6.9 (2–14)

FVIII, factor VIII; max, maximum; min, minimum.

Minor invasive procedures performed without FVIII treatment were associated with higher participant FVIII activity per CSA

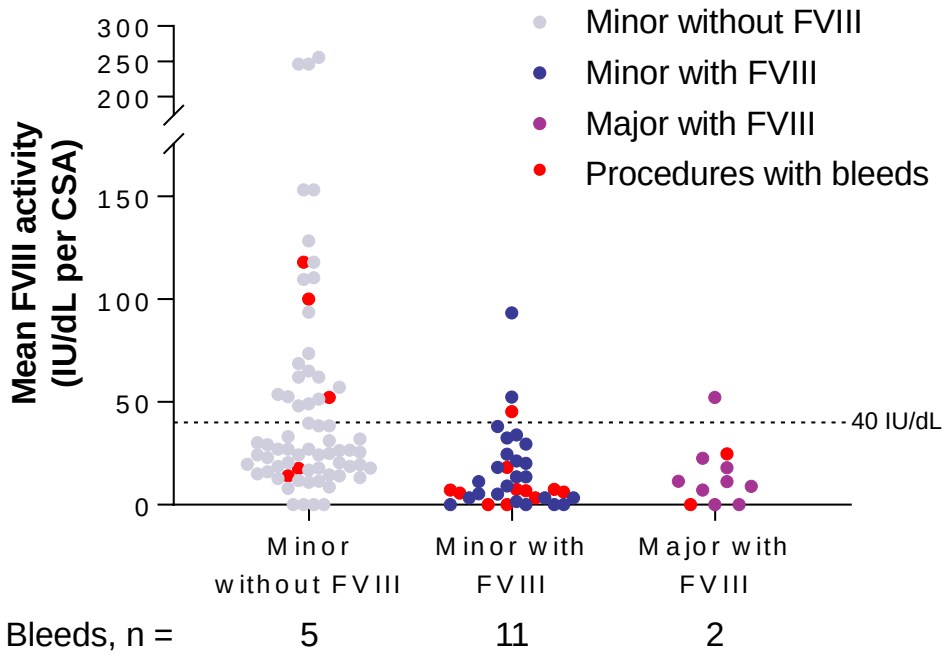




CSA, chromogenic substrate assay; FVIII, factor VIII.

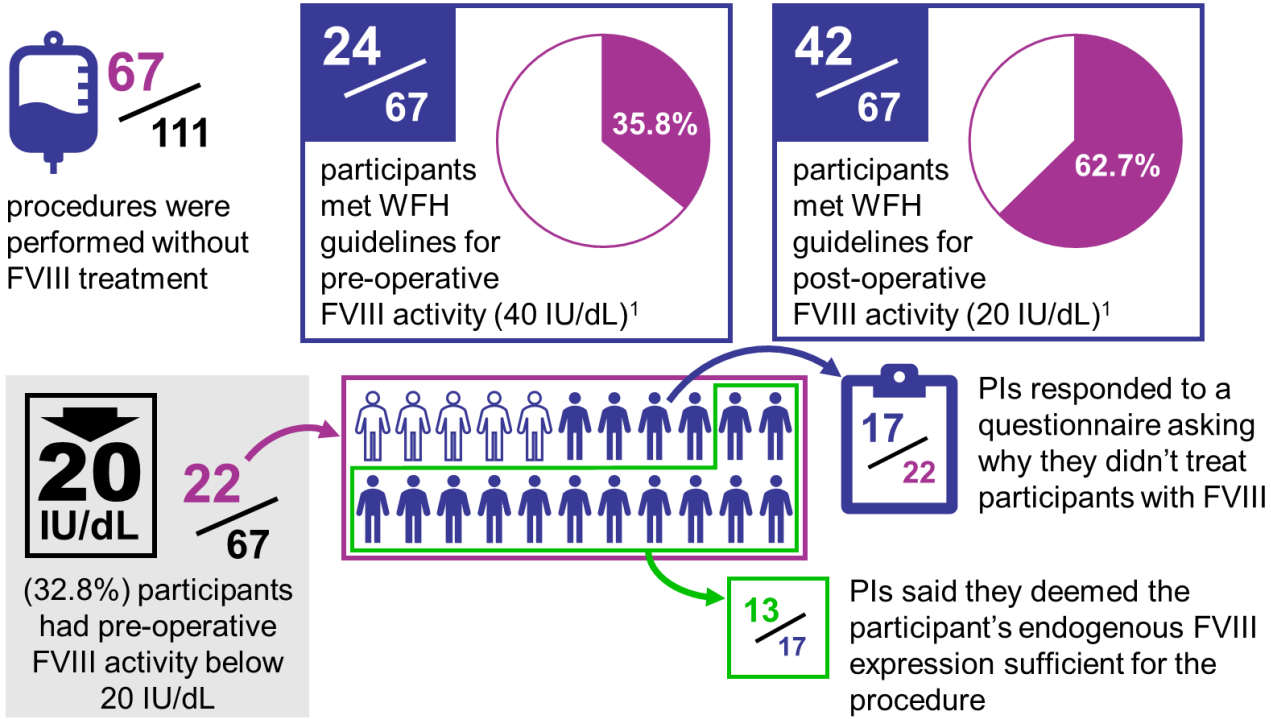
Relatively few invasive procedure–related bleeds occurred

- **There were 18 procedure-related bleeding episodes in 14 participants**
- Bleeding episodes were self-reported by participants
  - **13 required FVIII treatment**
    - Mean FVIII activity: 10.4 IU/dL
    - Median FVIII activity: 6.9 IU/dL
  - **5 did not require FVIII treatment**
    - Mean FVIII activity: 60.4 IU/dL
    - Median FVIII activity: 52.1 IU/dL



CSA, chromogenic substrate assay; FVIII, factor VIII.

Effective haemostatic control was possible for participants of the GENEr8-1 trial



FVIII, factor VIII; PI, principal investigator; WFH, World Federation of Hemophilia.

1. Srivastava A, et al. *Haemophilia*. 2020;26(suppl 6):1-158.

Conclusions

- In the GENEr8-1 clinical trial of valoctocogene roxaparvovec for severe haemophilia A, 67 out of 111 invasive procedures were performed without FVIII treatment
  - Most minor invasive procedures (62/67) were safely performed without bleeding events
  - For minor invasive procedures, FVIII treatment was associated with lower participant pre-operative endogenous FVIII activity
- PI questionnaire responses reflect the nature of personalized medicine with valoctocogene roxaparvovec
  - Most PIs and participants had case-by-case discussions about the use of FVIII treatment for procedures, given the participant's endogenous FVIII activity achieved with gene therapy and the type of procedure
- The data from this study, and the opinions reflected in the PI questionnaire, suggest that valoctocogene roxaparvovec provides effective haemostatic control for up to 2 years even with FVIII activity below WFH guidelines

FVIII, factor VIII; PI, principal investigator; WFH, World Federation of Hemophilia.

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