40

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

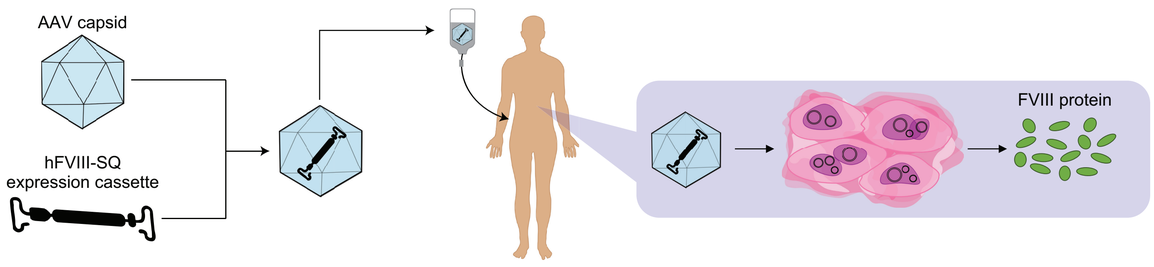
Rauch A[1], Quon DV[2], Wang JD[3], Wang M[4], Pepperell D[5], Park YS[6], Kenet G[7], Mahlangu J[8], Khoo T-L[9], Robinson TM[10], Chavele K-M[10], Pipe SW[11]

[1]Centre Hospitalier Régional Universitaire de Lille, Lille, France; [2]Orthopaedic Hemophilia Treatment Center, Los Angeles, CA, USA; [3]Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan; [4]Hemophilia and Thrombosis Center, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [5]Department of Haematology, Fiona Stanley Hospital, Murdoch, WA, Australia; [6]Kyung Hee University Hospital at Gangdong, Seoul, South Korea; [7]The National Hemophilia Center, and Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Tel Aviv University, Tel Aviv, Israel; [8]Hemophilia Comprehensive Care Center, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand and NHLS, Johannesburg, South Africa; [9]Haematology Department, Haemophilia Treatment Center, The Royal Prince Alfred Hospital, Sydney, NSW, Australia; [10]BioMarin Pharmaceutical Inc., Novato, CA, USA; [11]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA

Background

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

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a factor VIII (FVIII) coding sequence to hepatocytes using a recombinant AAV5 vector, enabling endogenous FVIII production in people with severe haemophilia A[1-4]
- A decrease in need for FVIII concentrates in case of invasive procedure is likely to be observed in patients responding to valoctocogene roxaparvovec according to endogenous FVIII level
- 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 principal investigator (PI) decisions



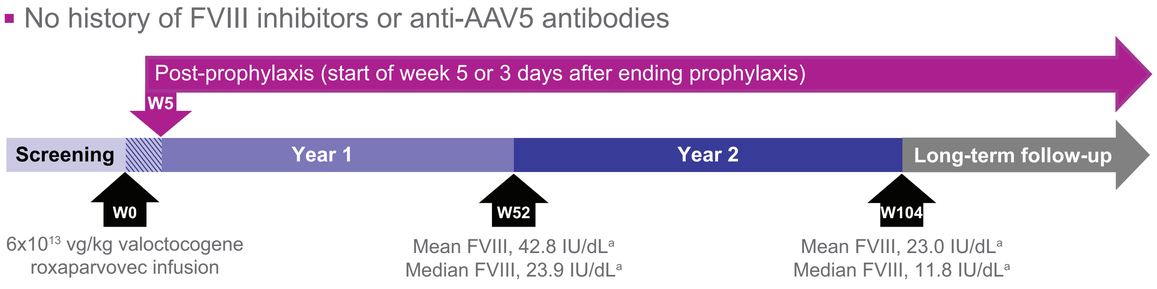
AAV5, adeno-associated virus serotype 5; hFVIII-SQ, human FVIII, SQ variant.

Methods

Phase 3 GENEr8-1 study design

Eligible participants

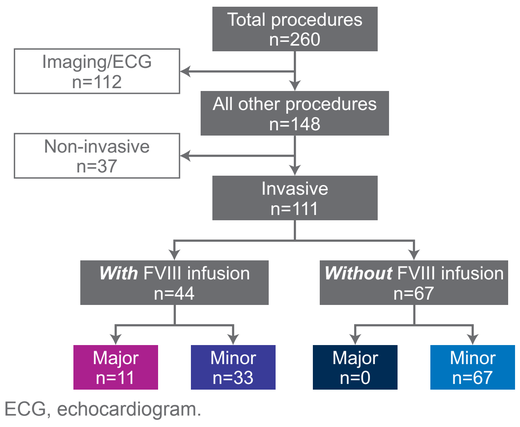
- Participants directly enrolled or were rolled over from the non-interventional study BMN 270-902
- According to protocol, the decision to use or not FVIII concentrate substitutive treatment in case of invasive procedure (classified as major or minor according to usual criteria) and its modalities remained at the discretion of investigator. Biologically, endogenous FVIII activity (at the closest measurement to each invasive procedure) was assessed per chromogenic assay
- 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.

Procedures performed during GENEr8-1

- In total, 77 participants underwent 260 total procedures
- Types of procedures[6]
  - 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.

Results

Baseline demographics and characteristics of ITT population

Baseline characteristics[4]	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.

Perioperative management for participants in GENEr8-1

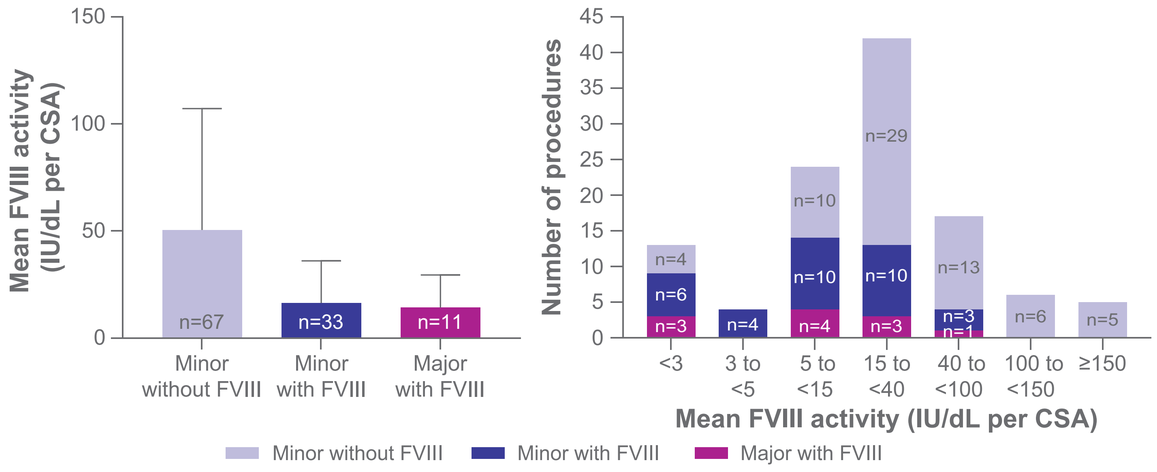
- Major invasive procedures were performed with FVIII treatment regardless of participant FVIII level
- Compared with minor procedures, major procedures were associated with a higher:
  - FVIII dose
  - Number of FVIII infusions
  - Days of post-operative FVIII treatment

	Minor invasive procedures (N=33)	Major invasive procedures* (N=11)
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)

*6 patients underwent a total of 11 major procedures.
Max, maximum; min, minimum.

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

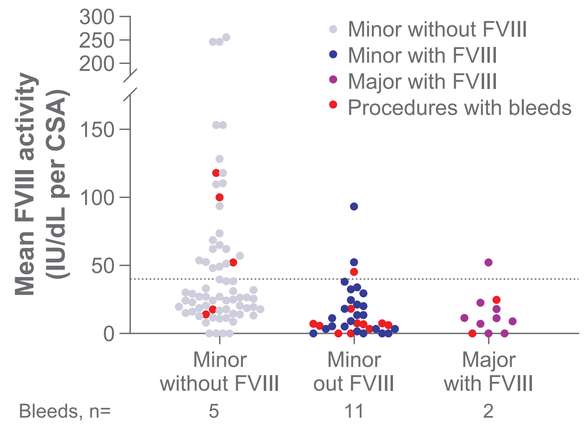
- By the 2-year data cutoff, 111 invasive procedures were performed in 77 participants. Of 111 invasive procedures, 44 required additional FVIII treatment and 67 did not



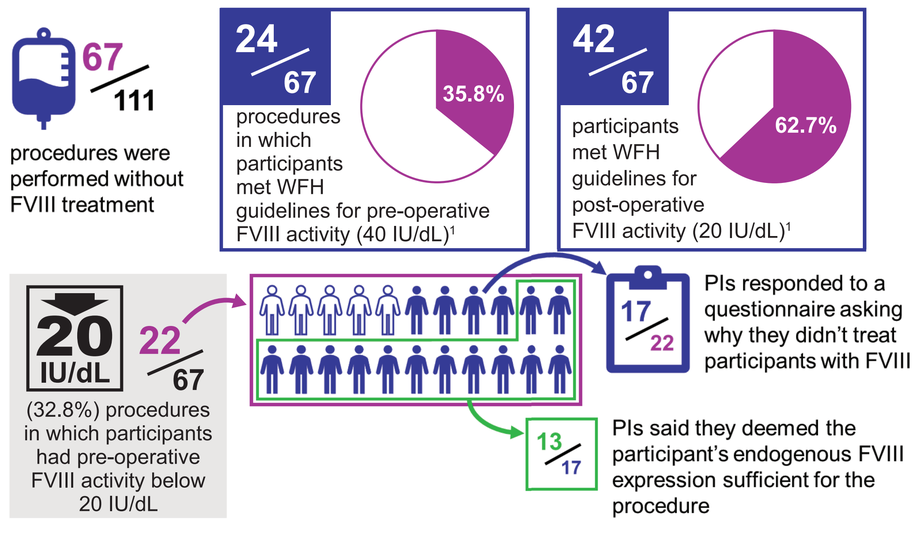
n = number of procedures. CSA, chromogenic substrate assay.

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



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



Conclusions

- In GENEr8-1 clinical trial of valoctocogene roxaparvovec for severe haemophilia A, 67 of 111 invasive procedures performed by the 2-year data cutoff did not require any additional FVIII concentrate treatment
  - 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 present analysis, in line with the investigators' responses, shows that valoctocogene roxaparvovec provides effective haemostatic control over the 2 years analysed here and underlines the importance of personalized medicine

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Conflict of interest

Antoine Rauch reports research support/PI Grant from CSL Behring, LFB, Roche/Chugai; investigator in clinical trials with BioMarin Pharmaceutical Inc., Bioverativ, CSL Behring, Shire/Takeda, Roche, Sobi; scientific advisory board with BioMarin Pharmaceutical Inc., CSL Behring, LFB, Octapharma, Roche, Sobi. **Doris V Quon** reports consulting fees from Roche/Genentech, Novo Nordisk, BioMarin Pharmaceutical Inc., Bayer, Takeda Pharmaceutical Company, Octapharma, and Sanofi; has participated as a clinical trial investigator for BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, Roche/Genentech, Shire/Takeda, and uniQure; and has received speaker honoraria and travel support from Roche/Genentech, Novo Nordisk, Takeda, Sanofi, and BioMarin Pharmaceutical Inc. **Jiaan-Der Wang** reports consulting fees from Bayer, Novo Nordisk, Alnylam, Pfizer, Chugai, and Sanofi; and serves as a clinical trial investigator for BioMarin Pharmaceutical Inc., Pfizer, Sanofi, Bayer, Novo Nordisk, and Chugai. **Michael Wang** reports consulting fees from BioMarin Pharmaceutical Inc., Bayer, Bioverativ, CSL Behring, Novo Nordisk, Genentech, Takeda, HEMA Biologics, and uniQure; and participation as a clinical trial investigator for BioMarin Pharmaceutical Inc., Bayer, Bioverativ, CSL Behring, Novo Nordisk, Genentech, Takeda, HEMA Biologics, uniQure, Pfizer/Spark, and Octapharma. **Dominic Pepperell** reports consulting fees from Sanofi and a travel grant from Pfizer. **Young Shil Park** reports research support from or participation as a principal investigator for BioMarin Pharmaceutical Inc., CSL Behring, Novo Nordisk, Sanofi, Takeda, Pfizer, and Chugai. **Gili Kenet** reports research support from Alnylam, Bayer, Opko Biologics, Pfizer, and Shire; and honoraria for consultancy from Alnylam, Bayer, Novo Nordisk, Pfizer, Roche, and Takeda. **Johnny Mahlangu** reports consulting payments from Catalyst BioSciences, CSL Behring, F. Hoffman-La Roche Ltd., Novo Nordisk, Spark Therapeutics, and Takeda; research support from and/or participation as a principal investigator for BioMarin Pharmaceutical Inc., CSL Behring, Novo Nordisk, F. Hoffman-La Roche Ltd., SOBI, and uniQure. **Teh-Liane Khoo** reports consulting fees from BioMarin Pharmaceuticals Inc., CSL Behring, Novo Nordisk, Roche/Genentech, and Sanofi; and has served as a clinical trial investigator for BioMarin Pharmaceutical Inc., Genentech/Roche, and Sanofi. **Steven W Pipe** reports consulting fees from Apcintex, ASC Therapeutics, Bayer, BioMarin Pharmaceutical Inc., CSL Behring, HEMA Biologics, Freeline Therapeutics, LFB, Novo Nordisk, Pfizer, Regeneron/Intellia, Roche/Genentech, Sanofi, Spark Therapeutics, Takeda, and uniQure; and service as a clinical trial investigator for BioMarin Pharmaceutical Inc., Freeline Therapeutics, Genentech/Roche, Sanofi, Spark Therapeutics, and uniQure. **Tara M Robinson** and **Konstantia-Maria Chavele** are employees and stockholders of BioMarin Pharmaceutical Inc..

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