Efficacy and safety of valoctocogene roxaparvovec adeno-associated virus gene transfer for severe hemophilia A:

Results from the phase 3 GENEr8-1 trial

Margareth C Ozelo,[1] *Johnny Mahlangu,*[2] *K John Pasi,*[3] *Adam Giermasz,*[4] *Andrew D Leavitt,*[5] *Michael Laffan,*[6] *Emily Symington,*[7] *Doris V Quon,*[8] *Jiaan-Der Wang,*[9] *Kathelijne Peerlinck,*[10] *Steven Pipe,*[11] *Bella Madan,*[12] *Nigel S Key,*[13] *Glenn F Pierce,*[14] *Brian O'Mahony,*[15,16] *Radoslaw Kaczmarek,*[17,18] *Adebayo Lawal,*[19] *Mei Huang,*[19] *Wing Yen Wong,*[19] *Benjamin Kim,*[19] *for the GENEr8-1 Trial Group*

[1]Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, SP, Brazil; [2]Hemophilia Comprehensive Care Center, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand and NHLS, Johannesburg, South Africa; [3]Barts and the London School of Medicine and Dentistry, London, UK; [4]Hemophilia Treatment Center, University of California Davis, Sacramento, CA, USA; [5]University of California San Francisco, San Francisco, CA, USA; [6]Centre for Haematology, Imperial College London, London, UK; [7]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [8]Orthopaedic Hemophilia Treatment Center, Los Angeles, CA, USA; [9]Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan; [10]Department of Vascular Medicine and Haemostasis and Haemophilia Centre, University Hospitals Leuven, Leuven, Belgium; [11]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA; [12]Guy's & St. Thomas' NHS Foundation Trust, London, UK; [13]UNC Blood Research Center, University of North Carolina, Chapel Hill, NC, USA; [14]Independent Consultant, La Jolla, CA, USA; [15]Irish Haemophilia Society, Dublin, Ireland; [16]Trinity College, Dublin, Ireland; [17]Department of Pediatrics, Indiana University School of Medicine, IUPUI-Wells Center for Pediatric Research, Indianapolis, IN, USA; [18]Laboratory of Glycobiology, Hirszfeld Institute of Immunology and Experimental Therapy, Wroclaw, Poland; [19]BioMarin Pharmaceutical Inc., Novato, CA, USA

Disclosures for Margareth Ozelo

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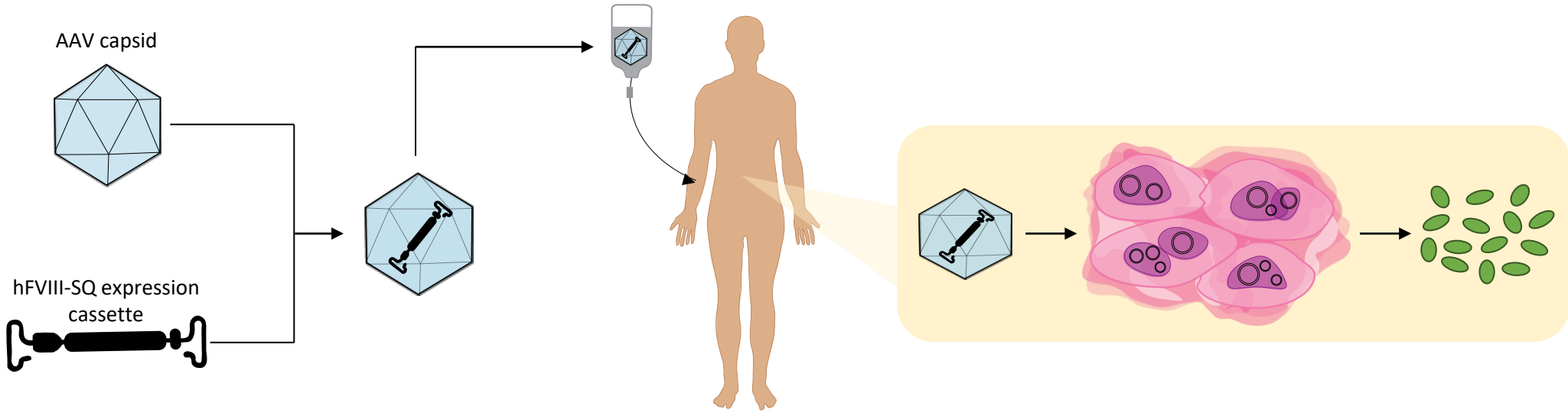
Scientific Advisory Board	**Bayer, BioMarin Pharmaceutical, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda**

Valoctocogene roxaparvovec gene therapy for severe hemophilia A

- Hemophilia A is an X-linked bleeding disorder caused by deficiency in coagulation FVIII
- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence to hepatocytes, enabling FVIII production in people with hemophilia A[1–3]
  - In a phase 1/2 trial, participants had sustained reduction in bleeding and FVIII use up to 4 years[1–3]
- GENEr8-1 (NCT03370913) is an open-label, single-arm, multicenter phase 3 trial evaluating efficacy and safety of valoctocogene roxaparvovec in adult men with severe hemophilia A



1. Rangarajan S, et al. *N Engl J Med*. 2017;377(26):2519–2530; 2. Pasi KJ, et al. *N Engl J Med.* 2020;382(1):29–40; 3. Pasi KJ, et al. *Haemophilia*. 2020;26(S4):151.
AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; ITR, inverted terminal repeat.

Phase 3 GENEr8-1 study design

Eligible participants (directly enrolled or rolling over from 270-902)

- Adult men with severe hemophilia A (FVIII ≤1 IU/dL)
- Previously receiving FVIII prophylaxis
- No history of FVIII inhibitors or anti-AAV5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

Primary efficacy endpoint
Change from baseline in FVIII activity

Safety

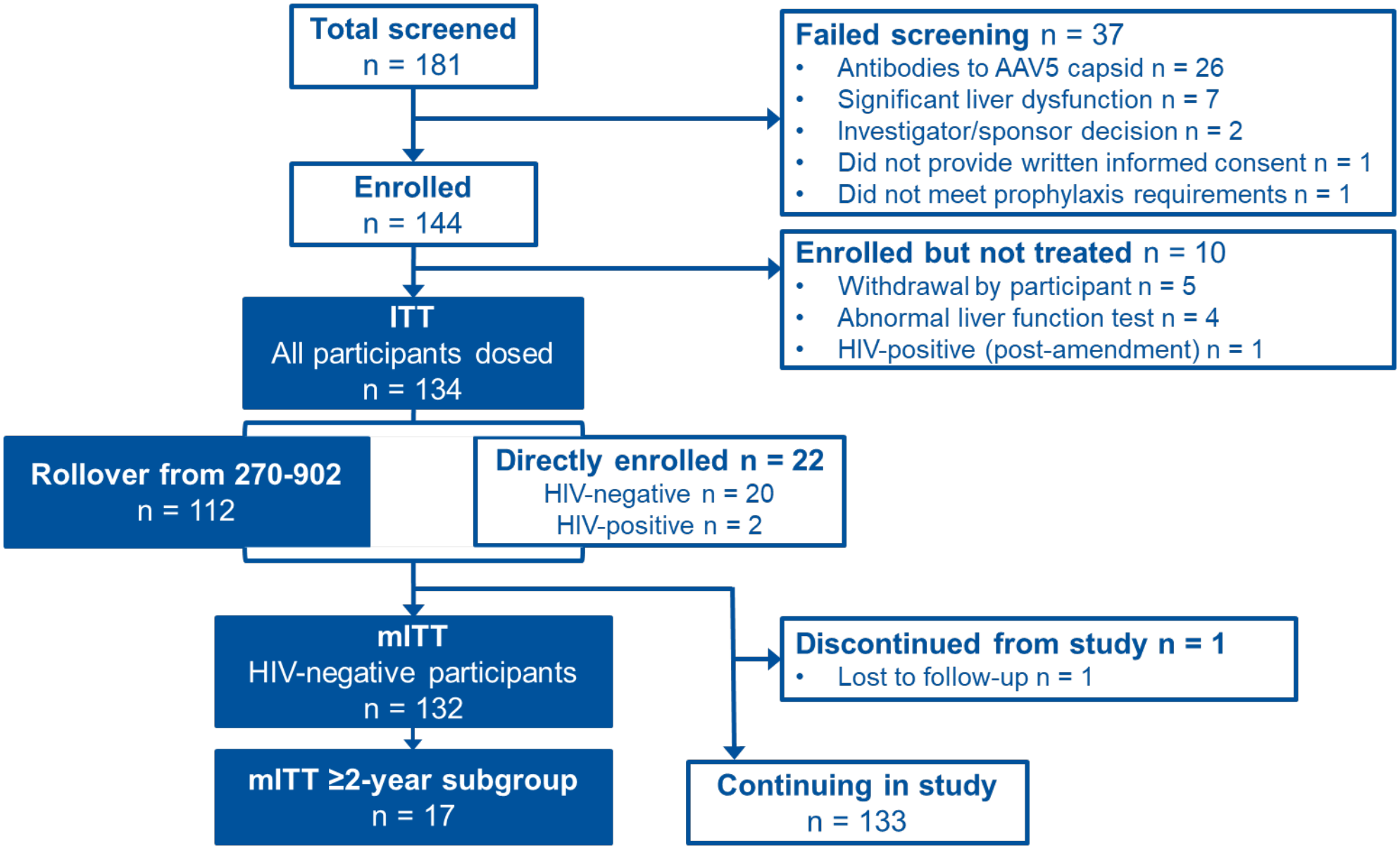
$6x10^{13}$ vg/kg valoctocogene roxaparvovec infusion

Secondary efficacy endpoints (after week 4)

- Change from baseline in annualized FVIII utilization rate
- Change from baseline in the annualized number of bleeding episodes requiring FVIII treatment (tested hierarchically for noninferiority and then superiority)

AAV5, adeno-associated virus serotype 5; ABR, annualized bleeding rate; FVIII, factor VIII.

Participant disposition



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; HIV, human immunodeficiency virus; ITT, intent-to-treat; mITT, modified ITT.

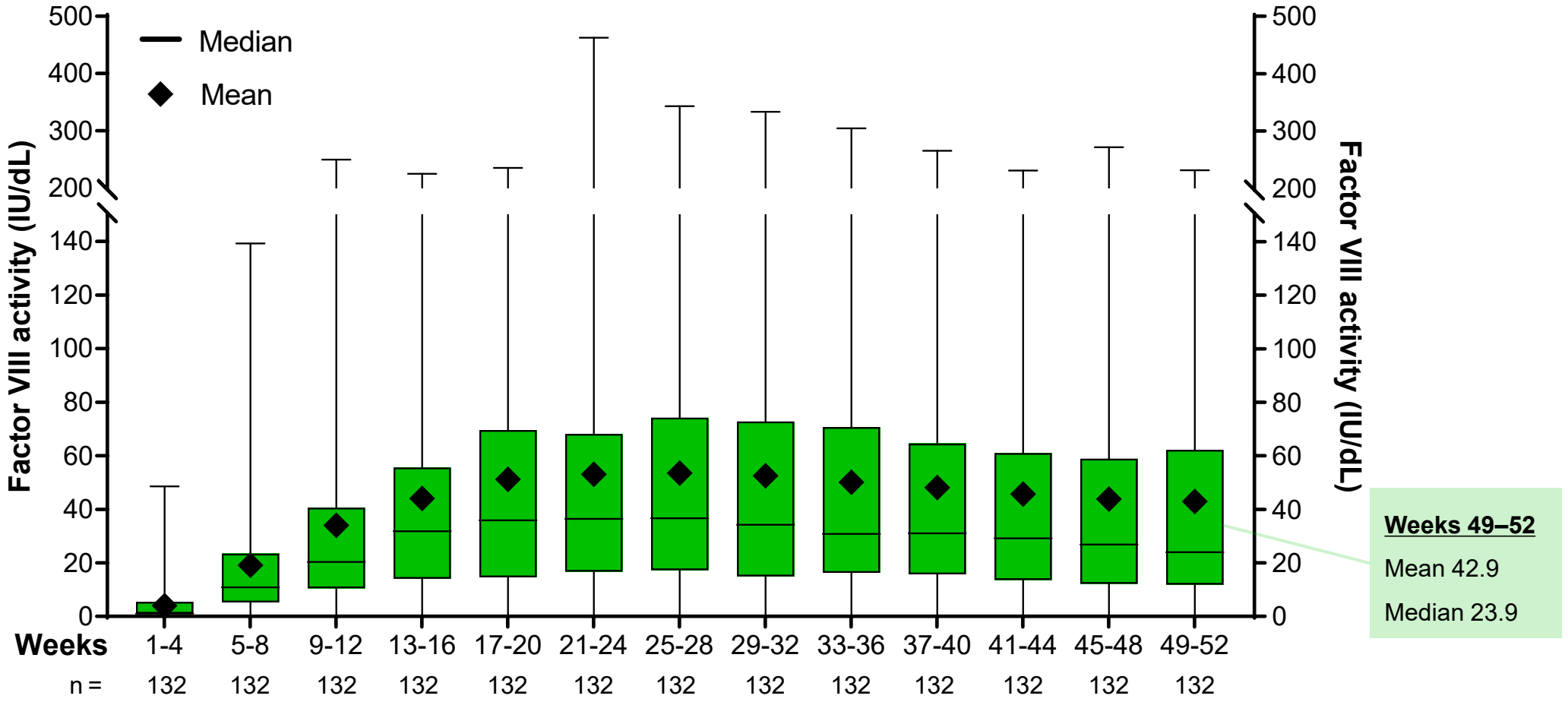
Baseline demographics and characteristics

Baseline Characteristics	mITT ≥2-year n = 17	Rollover population n = 112	mITT n = 132	ITT n = 134
Age, years, mean ± SD	29.5 ± 6.0	31.8 ± 10.6	31.4 ± 10.1	31.7 ± 10.3
Race, n (%)				
White	14 (82.4)	78 (69.9)	94 (71.2)	96 (71.6)
Asian	1 (5.9)	17 (15.2)	19 (14.4)	19 (14.2)
Black or African American	1 (5.9)	14 (12.5)	15 (11.4)	15 (11.2)
Hawaiian or Pacific Islander	0	1 (0.9)	1 (0.8)	1 (0.7)
Not provided	1 (5.9)	2 (1.8)	3 (2.3)	3 (2.2)
Hispanic or Latino ethnicity, n (%)	1 (5.9)	5 (4.5)	7 (5.3)	7 (5.2)
BMI, kg/m^2, mean ± SD	26.4 ± 3.8	25.2 ± 4.7	25.3 ± 4.6	25.3 ± 4.6
Previous disease, n (%)				
Hepatitis B	1 (5.9)	17 (15.2)	18 (13.6)	20 (14.9)
Hepatitis C	6 (35.3)	33 (29.5)	39 (29.5)	41 (30.6)
HIV	0	0	0	2 (1.5)
Number of problem joints,* n (%)				
0	10 (58.8)	82 (73.2)	95 (72.0)	97 (72.4)
1	4 (23.5)	13 (11.6)	17 (12.9)	17 (12.7)
2	0	9 (8.0)	9 (6.8)	9 (6.7)
3	2 (11.8)	6 (5.4)	8 (6.1)	8 (6.0)
>3	1 (5.9)	2 (1.8)	3 (2.3)	3 (2.2)

*Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.
BMI, body mass index; ITT, intent-to-treat; mITT, modified ITT; SD, standard deviation.

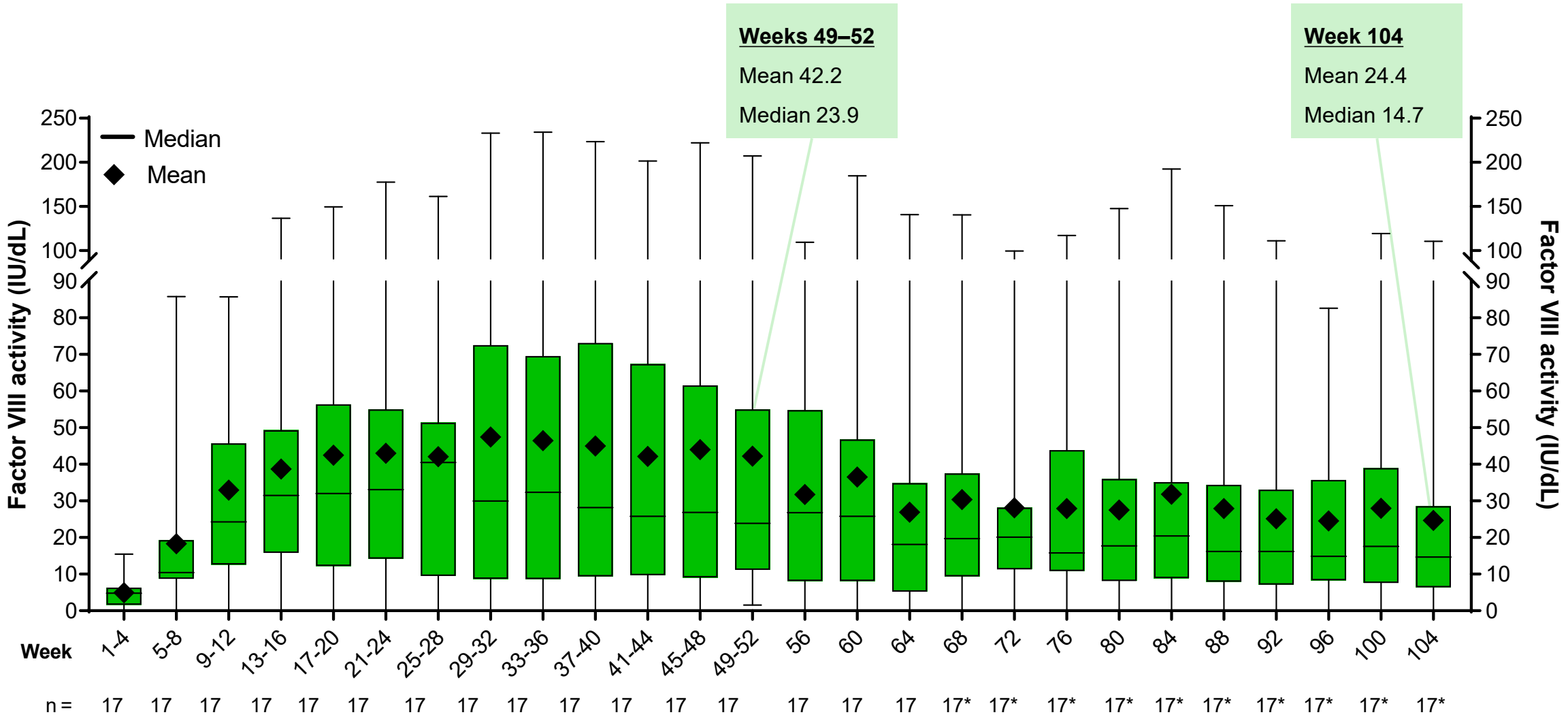
FVIII activity over 52 weeks in the mITT

- At weeks 49–52, mean (95% CI) change from baseline in FVIII activity was **41.9 (34.1–49.7) IU/dL** (*P* <0.001)
  - Median (Q1, Q3) change from baseline was **22.9 (10.9, 61.3) IU/dL**



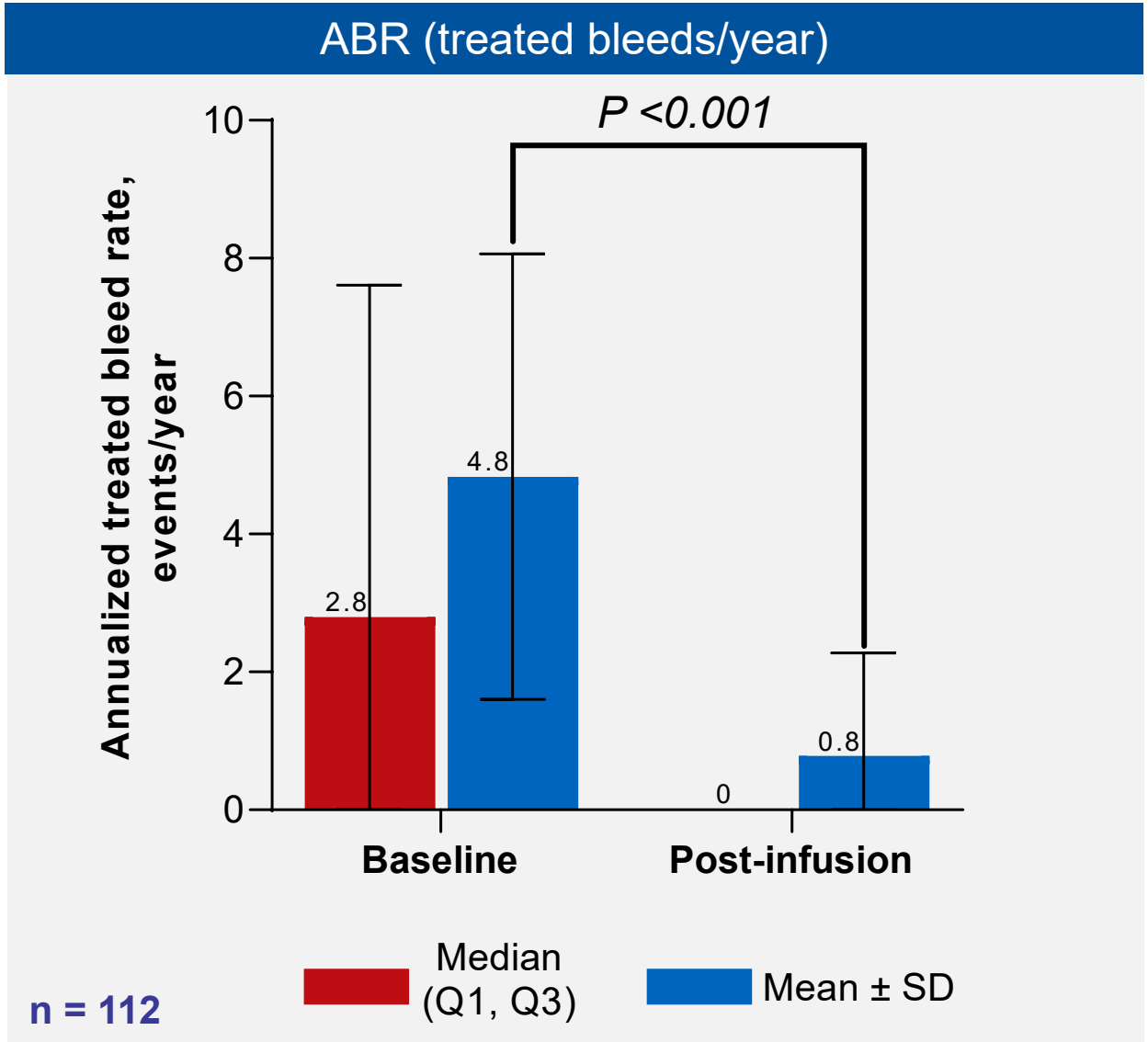
P value is from a 2-sided 1-sample t-test against the null hypothesis that the change from baseline is 0. FVIII activity was measured using the chromogenic substrate assay. FVIII activity values were excluded if obtained within 72 hours of FVIII replacement therapy. Values below the lower limit of quantitation of the assay (3 IU/dL) were imputed as 0 IU/dL. Baseline values were imputed as 1 IU/dL. Boxes represent the interquartile range, whiskers represent the range, horizontal lines represent the median, and diamonds represent the mean. CI, confidence interval; FVIII, factor VIII; mITT, modified intent-to-treat.

FVIII activity over 104 weeks in the mITT dosed ≥2 years prior



*One participant was lost to follow-up at week 66; his missing data were imputed as 0 IU/dL using last observation carried forward. FVIII activity was measured using the chromogenic substrate assay. FVIII activity values were excluded if obtained within 72 hours of FVIII replacement therapy. Values below the lower limit of quantitation of the assay (3 IU/dL) were imputed as 0 IU/dL. Baseline values were imputed as 1 IU/dL. Boxes represent the interquartile range, whiskers represent the range, horizontal lines represent the median, and diamonds represent the mean. FVIII, factor VIII; mITT, modified intent-to-treat.

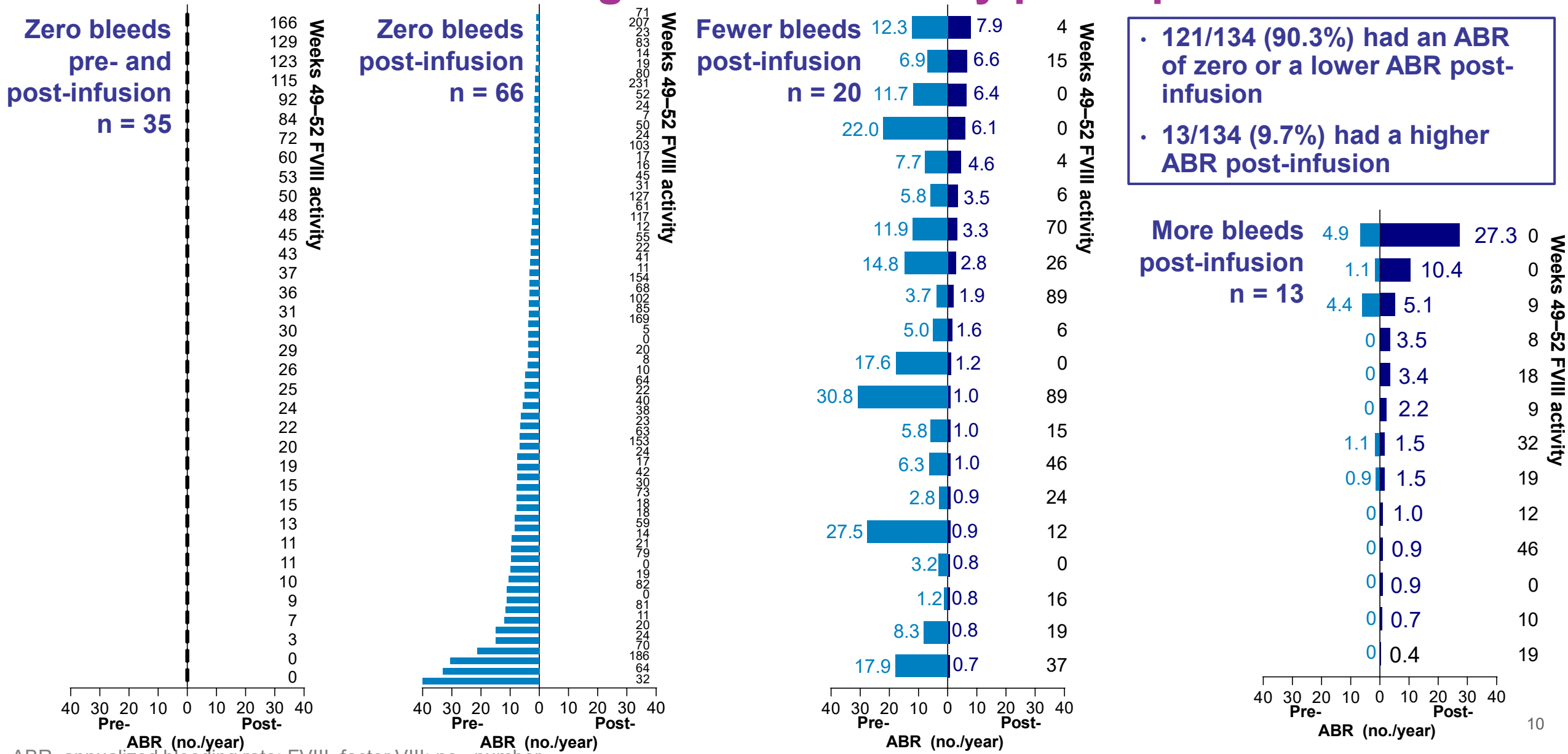
Reduction in annualized treated bleeding rate in rollover population



- Mean change in ABR was a decrease of 4.1 treated bleeding events/year
  - 95% CI: −5.3 to −2.8
- 83.8% reduction from baseline
- Superiority to FVIII prophylaxis demonstrated (P <0.001)
- Percentage of participants with zero treated bleeds increased from 32% on FVIII prophylaxis to 80% after week 4 post-infusion

Post-infusion is defined as after week 4. *P*-value is from a 2-sided, 1-sample t-test against the null hypothesis that the change from baseline is 0.
ABR, annualized bleeding rate; CI, confidence interval; FVIII, factor VIII; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Annualized treated bleeding rates in all study participants



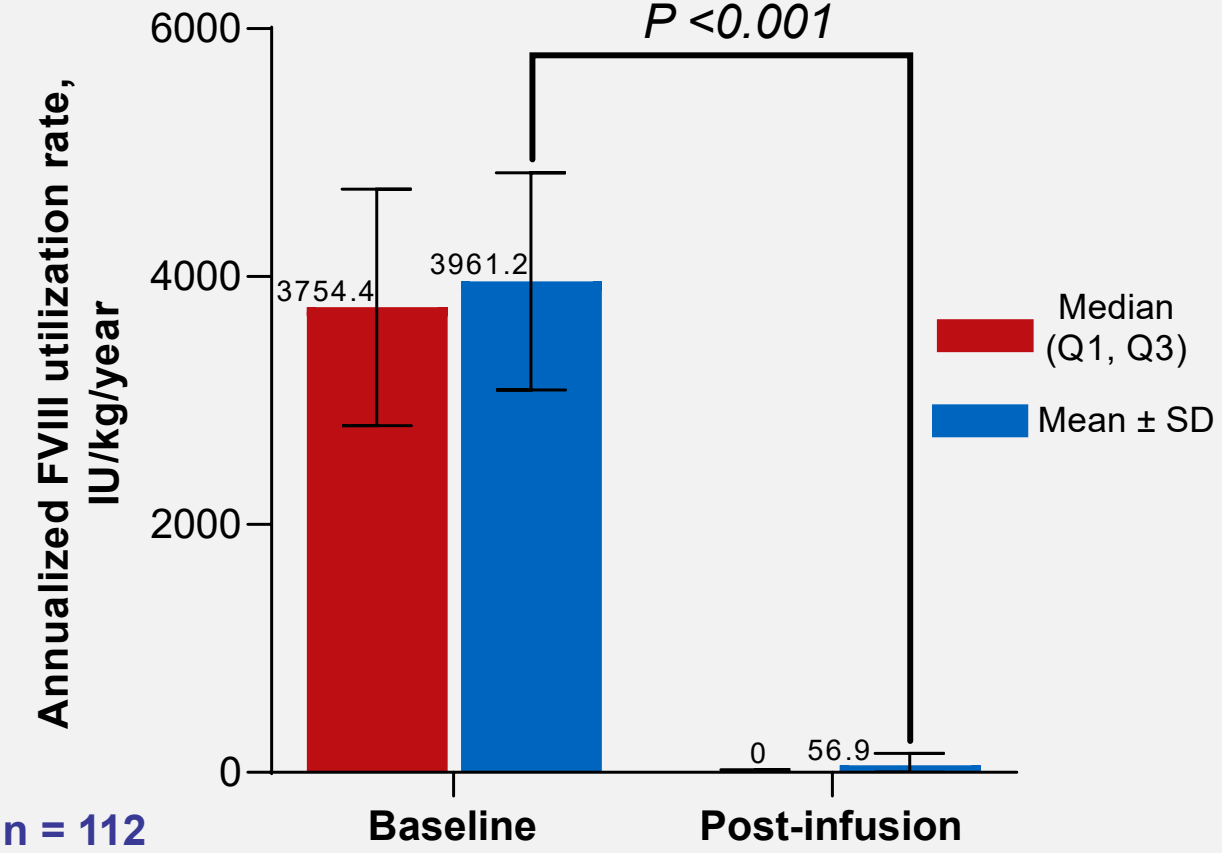
- 121/134 (90.3%) had an ABR of zero or a lower ABR post-infusion
- 13/134 (9.7%) had a higher ABR post-infusion

ABR, annualized bleeding rate; FVIII, factor VIII; no., number.

Reduction in annualized FVIII utilization and infusion rates

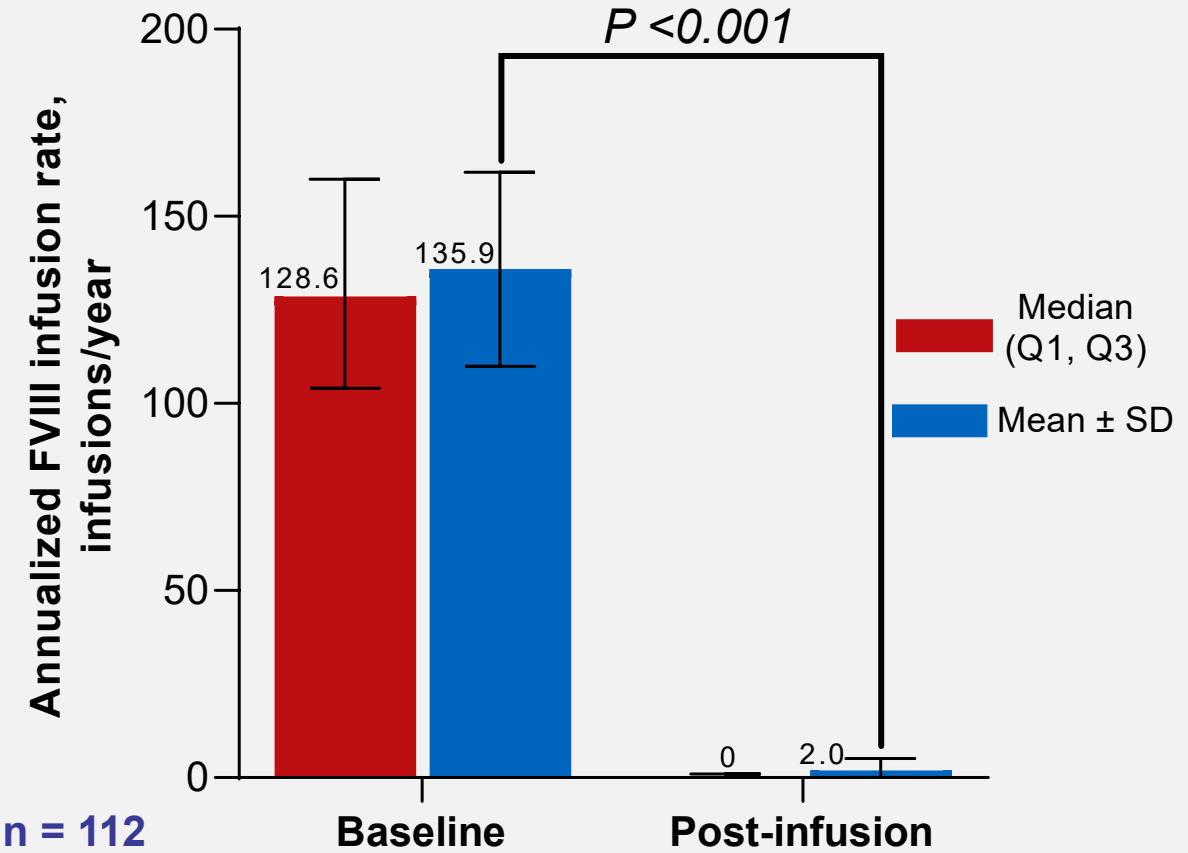
FVIII utilization rate (IU/kg/year)

Mean change was a decrease of 3904 IU/kg/year (98.6% reduction); 95% CI: −4233 to −3576



FVIII infusion rate (infusions/year)

Mean change was a decrease of 134 infusions/year (98.6% reduction); 95% CI: −144 to −124



Post-infusion is defined as after week 4. *P*-value is from a 2-sided 1-sample t-test against the null hypothesis that the change from baseline is 0.
CI, confidence interval; FVIII, factor VIII; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Safety

- No participants withdrew due to AEs, developed FVIII inhibitors, or experienced thrombosis
- Infusion reactions were defined as any AEs occurring within 48 hours post-infusion; most common were nausea (14.2%), fatigue (7.5%), and headache (6.0%)
- Systemic hypersensitivity during/following infusion was mitigated by slowing or pausing infusion and treating with supportive medications, as indicated
  - Four (3.0%) participants completed infusion after interruption

	ITT (n = 134)	
	n	%
Any AE	134	100
AEs occurring in ≥20%		
ALT increased	115	85.8
Headache	51	38.1
Nausea	50	37.3
AST increased	47	35.1
Arthralgia	39	29.1
Fatigue	37	27.6
Acne	36	26.9
Insomnia	28	20.9
Upper respiratory tract infection	27	20.1
Any serious AE	22	16.4
Any AE Grade ≥3	35	26.1
Any treatment-related AE	123	91.8
Any treatment-related serious AE	5	3.7
AEs of special interest		
ALT increased	115	85.8
Potential Hy's law case	0	0
Infusion-related reactions	50	37.3
Systemic hypersensitivity	7	5.2
Anaphylactic/anaphylactoid reactions	3	2.2
Thromboembolic events	0	0
Development of FVIII inhibitors	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FVIII, factor VIII; ITT, intent-to-treat.

ALT elevation and corticosteroids

- ALT elevation was the most common AE
- Overall, 79% of participants received corticosteroids per protocol as treatment for ALT elevation
- Average duration of corticosteroid treatment was 33 weeks
- Of these, 72% had AEs related to corticosteroid use
- 29% of participants used other immunosuppressants (budesonide, tacrolimus, mycophenolate, methylprednisolone)

	ITT (n = 134)	
	n/N	%
Participants with AE of post-baseline ALT elevation	115/134	85.8
Total number of ALT elevations	318	
Grade 1	266/318	83.6
Grade 2	40/318	12.6
Grade 3	12/318	3.8
Serious AEs of ALT elevations	2/318	0.6
Participants with per-protocol corticosteroid use	106/134	79.1
Time from infusion to first corticosteroid course, wks		
Mean ± SD	10.9 ± 9.8	
Median (min, max)	8.1 (1, 66)	
Duration of corticosteroid therapy per participant, days		
Mean ± SD	234.5 ± 116.0	
Median (min, max)	230.0 (22, 551)	
AEs related to corticosteroid use	79/110	71.8
AEs related to corticosteroids occurring in ≥10%		
Acne	32/110	29.1
Insomnia	23/110	20.9
Cushingoid	16/110	14.5
Weight increased	16/110	14.5
Serious AEs related to corticosteroid use	3/110	2.7
Participants with use of other immunosuppressants	39/134	29.1

AE, adverse event; ALT, alanine aminotransferase; ITT, intent-to-treat; SD, standard deviation; wks, weeks.

Conclusions

- In the global phase 3 GENEr8-1 study of 134 participants with severe hemophilia A, valoctocogene roxaparvovec yielded sustained expression of endogenous FVIII
- The study met its primary efficacy endpoint of change from baseline in FVIII activity at weeks 49–52 and also met its secondary endpoints of change from baseline in annualized FVIII utilization and annualized treated bleeding episodes after week 4
- In an ad hoc analysis of 17 participants who had been dosed ≥2 years prior to data cutoff, the decline in FVIII levels from year 1 to year 2 was similar to that observed in the phase 1/2 trial
- ALT increase (85.8%), headache (38.1%), nausea (37.3%), and AST increase (35.1%) were the most common AEs; most events were of Grade 1 or 2
- In total, 79% of participants received corticosteroids for ALT elevations for an average duration of 33 weeks
- Overall, the risk/benefit profile of valoctocogene roxaparvovec appears favorable, and we look forward to learning more about long-term durability and safety as we continue to follow the participants in this trial

ClinicalTrials.gov, NCT03370913

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FVIII, factor VIII.

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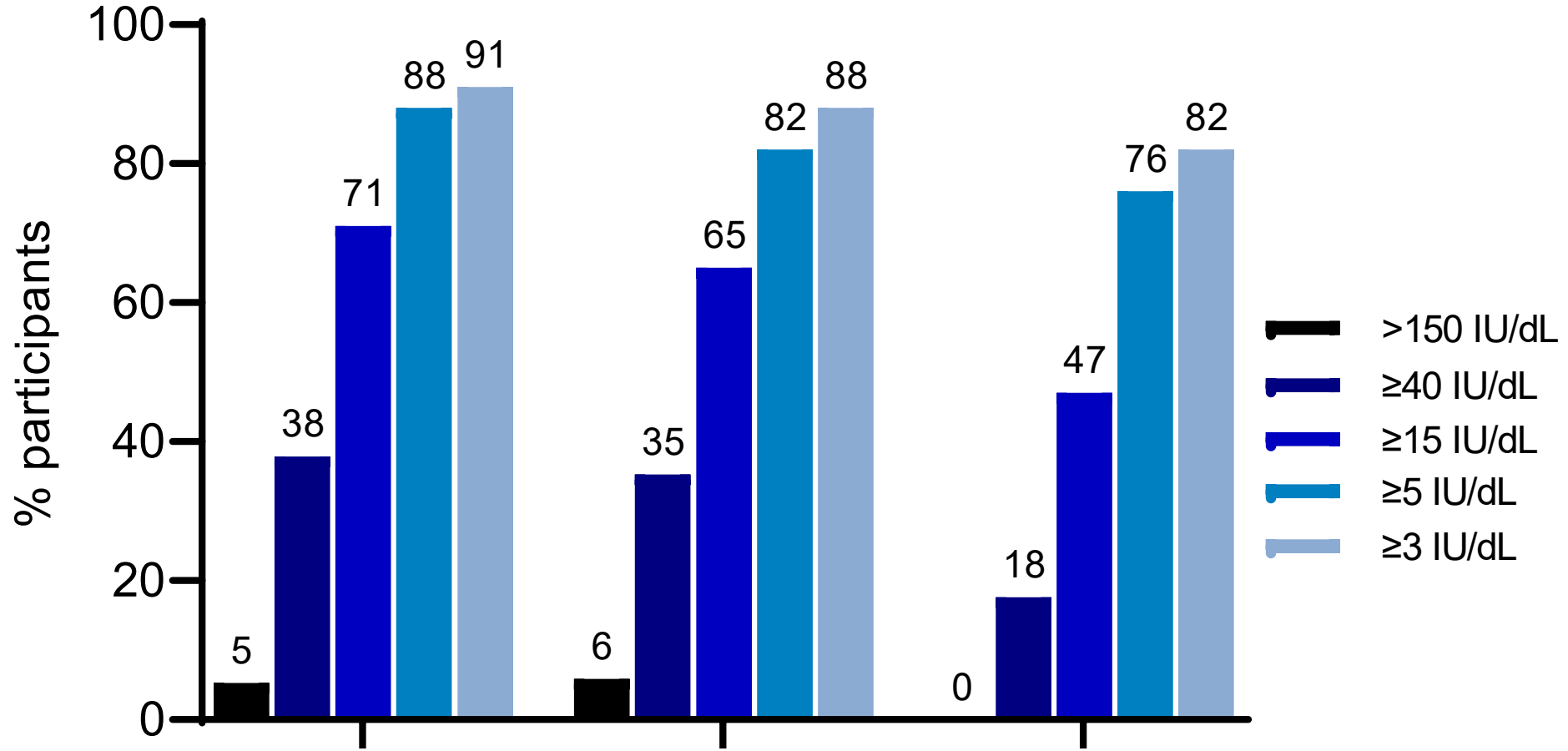
Summary of participant FVIII activity



	mITT (n = 132)	mITT ≥2-year (n = 17*)	
	Week 49–52	Week 49–52	Week 104
Mean ± SD	42.9 ± 45.5	42.2 ± 50.9	24.4 ± 29.2
Median (Q1, Q3)	23.9 (11.9, 62.3)	23.9 (11.2, 55.0)	14.7 (6.4, 28.6)

*For the participant lost to follow-up at week 66, FVIII activity at week 104 was imputed as <3 IU/dL. FVIII activity was measured using the chromogenic substrate assay.
FVIII, factor VIII; mITT, modified intent-to-treat; Q1, first quartile; Q3, third quartile; SD, standard deviation.