Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1

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OC 20.1

Disclosure – conflict of interest

I have the following potential conflict(s) of interest to report:

- **Receipt of grants/research support:** BioMarin Pharmaceutical Inc., Novo Nordisk, Novartis, Pfizer, F. Hoffman-La Roche Ltd, Sanofi, Spark Therapeutics, and Takeda
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Presentation learning objectives

In compliance with COI policy, ISTH requires that presenters list 1 to 3 learning objectives for each presentation:

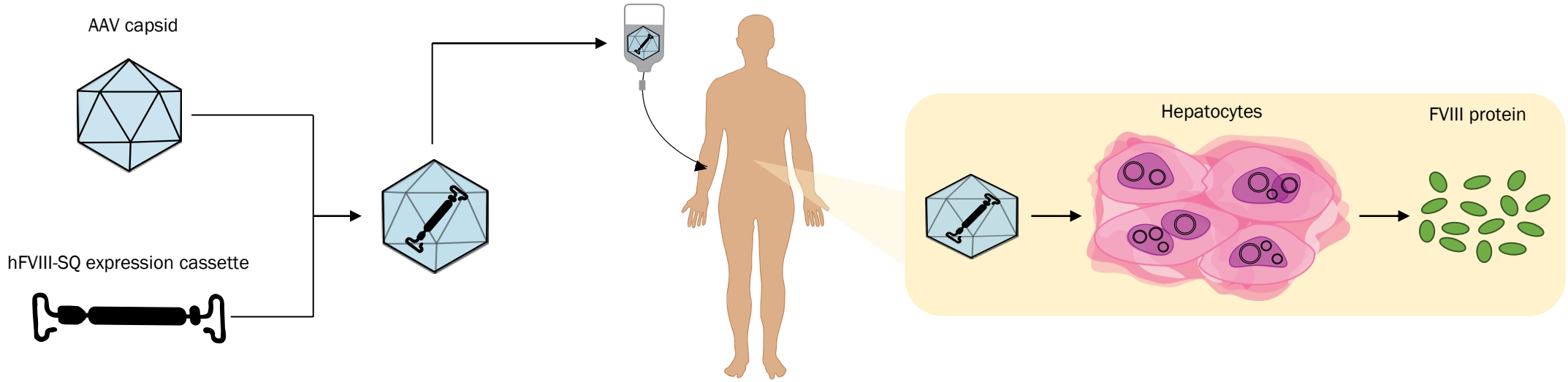
At the conclusion of this presentation, participants will be able to

- Describe 3-year efficacy, safety, and HRQoL results from the phase 3 GENEr8-1 trial of valoctocogene roxaparvovec gene therapy

HRQoL, health-related quality of life.

Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence that enables endogenous FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1,2]
- In the global, open-label, phase 3 GENEr8-1 trial, participants who received $6x10^{13}$ vg/kg valoctocogene roxaparvovec achieved FVIII activity that provided improved protection from bleeds compared with FVIII prophylaxis over 104 weeks[1,2]
- Here, we present outcomes after 3 years post-gene transfer



AAV, adeno-associated virus; FVIII, factor VIII; 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.

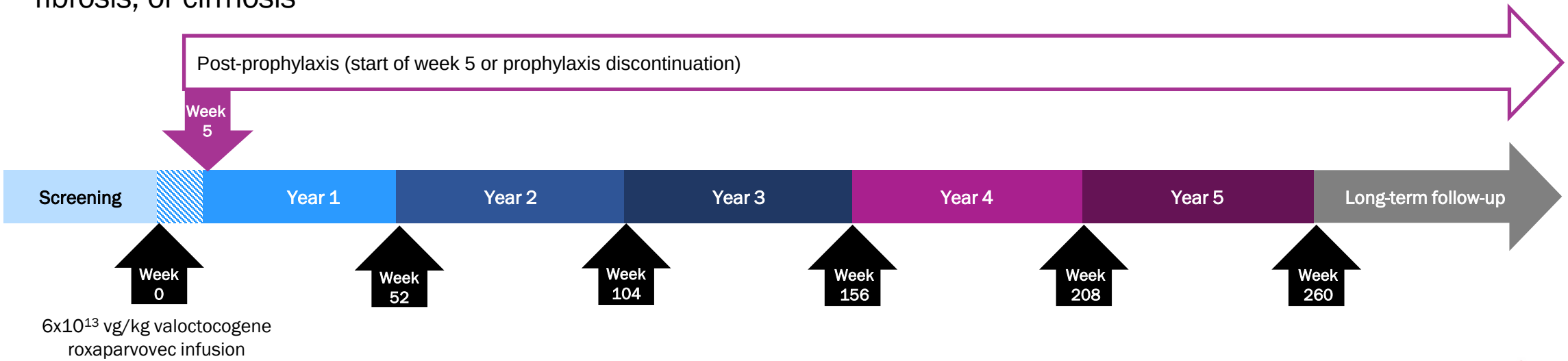
Phase 3 GENEr8-1 study design

Eligible participants (directly enrolled or rolling over from the non-interventional study BMN 270-902)

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

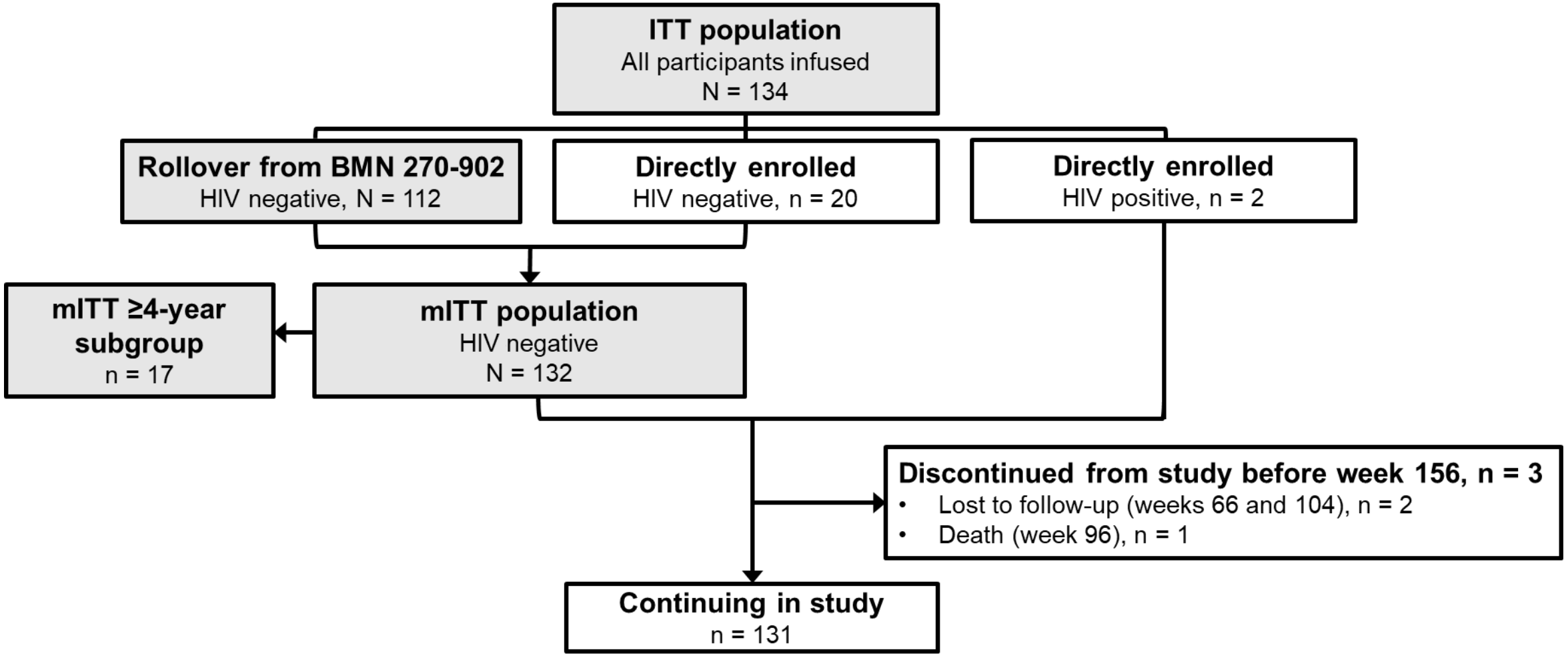
Endpoints

- Safety
- FVIII activity
- Change from baseline during post-prophylaxis
  - Annualized bleeding rate (treated and all bleeds)
  - Annualized FVIII utilization rate
- QoL



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; QoL, quality of life.

Participant disposition



HIV, human immunodeficiency virus; mITT, modified intent-to-treat; ITT, intent-to-treat.

No new safety signals in year 3

Participants, n (%)		ITT population N = 134 Year 1	Year 2	Year 3	Overall
AEs		134 (100)	112 (83.6)	103 (76.9)	134 (100)
SAEs		21 (15.7)	5 (3.7)	11 (8.2)	32 (23.9)
Treatment-related AEs		123 (91.8)	28 (20.9)	16 (11.9)	123 (91.8)
Corticosteroid-related AEs		80 (59.7)	9 (6.7)	0	81 (60.4)
AEs of special interest	ALT elevation	114 (85.1)	39 (29.1)	34 (25.4)	121 (90.3)
	ALT elevation Grade ≥3	11 (8.2)	1 (0.7)	0	11 (8.2)
	Potential Hy's law case	0	0	0	0
	Infusion-related reactions[a]	12 (9.0)	0	0	12 (9.0)
	Systemic hypersensitivity	7 (5.2)	0	0	7 (5.2)
	Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	3 (2.2)
	Thromboembolic events	0	0	0	0
	Anti-FVIII neutralizing antibodies	0	0	0	0
	Malignancy (except non-melanoma skin cancer)	0	0	1 (0.7)	1 (0.7)

- In year 3, the most common AE remains ALT elevation (25%), most Grade 1 and <ULN
  - No participants initiated corticosteroids after week 104
  - As of the data cutoff date, 3 participants were using corticosteroids for any indication
- No new Grade 3 AEs or SAEs related to treatment occurred in year 3
- No participants developed inhibitors or thromboembolic events

[a]Infusion-related reactions were defined as AEs occurring during valoctocogene roxaparvovec infusion or within 6 hours post-infusion.

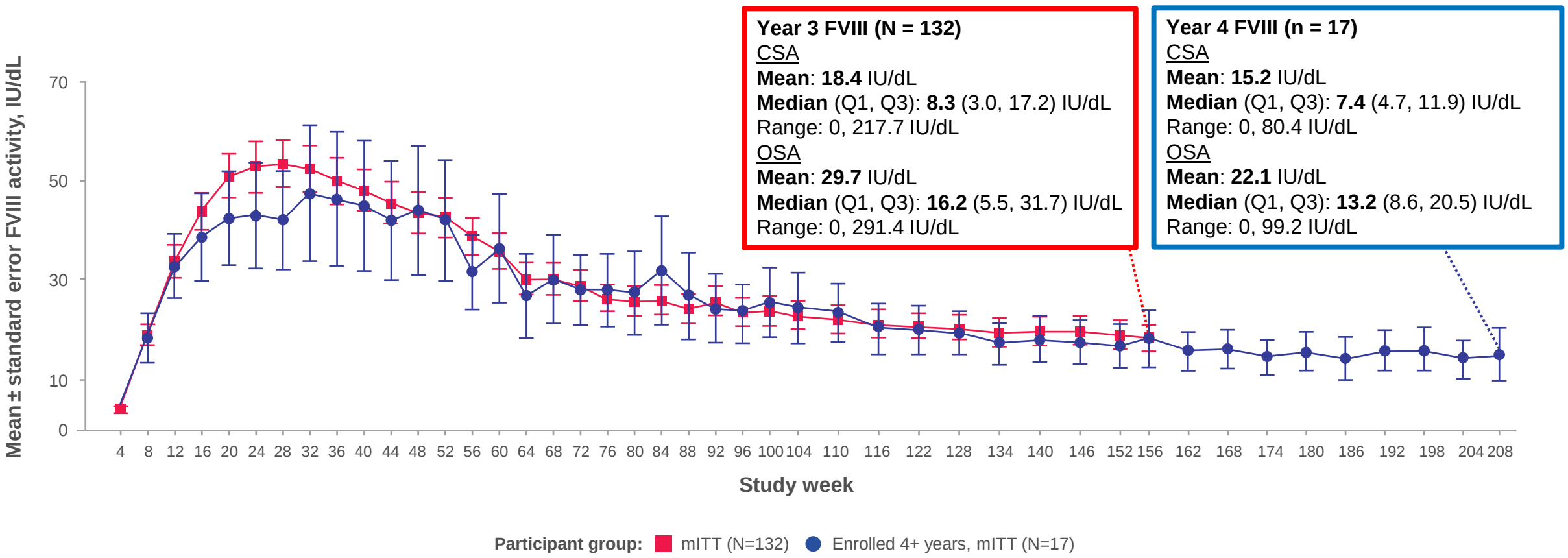
AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; ITT, intent-to-treat; SAE, serious adverse event; ULN, upper limit of normal.

SAE of B-cell acute lymphoblastic leukemia not linked to valoctocogene roxaparvovec

- Participant dosed almost 3 years ago with $6x10^{13}$ vg/kg valoctocogene roxaparvovec
- B-ALL diagnosed by bone marrow biopsy
- Genetic testing and whole genome sequencing were performed on leukemic and healthy blood cells
  - A known driver mutation for acute lymphoblastic leukemia was detected in 85% of bone marrow cells via standard-of-care genetic workup done at the clinical site and sequence data from a subsequent focused tumor gene panel
  - Assessment of valoctocogene roxaparvovec vector DNA demonstrated extremely low levels in 5 cell populations that underwent genomic analysis, with the lowest levels in tumor-containing samples
  - No vector–host integration sites were identified in the analysis of whole genome sequencing for all samples
- Based on these analyses, it is **very unlikely** that valoctocogene roxaparvovec played a role in the development of B-ALL in this study participant

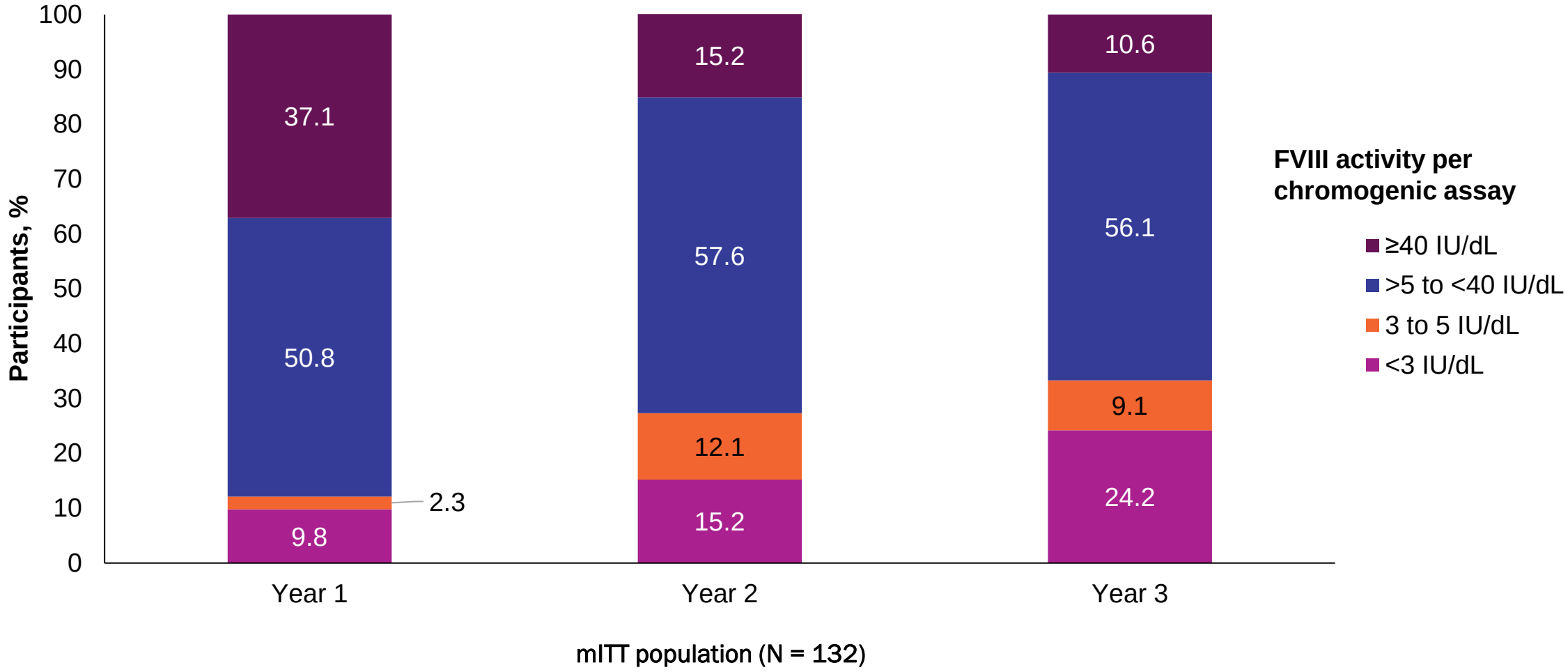
B-ALL, B-cell acute lymphoblastic leukemia; SAE, serious adverse event.

FVIII activity persists at hemostatic levels for up to 4 years



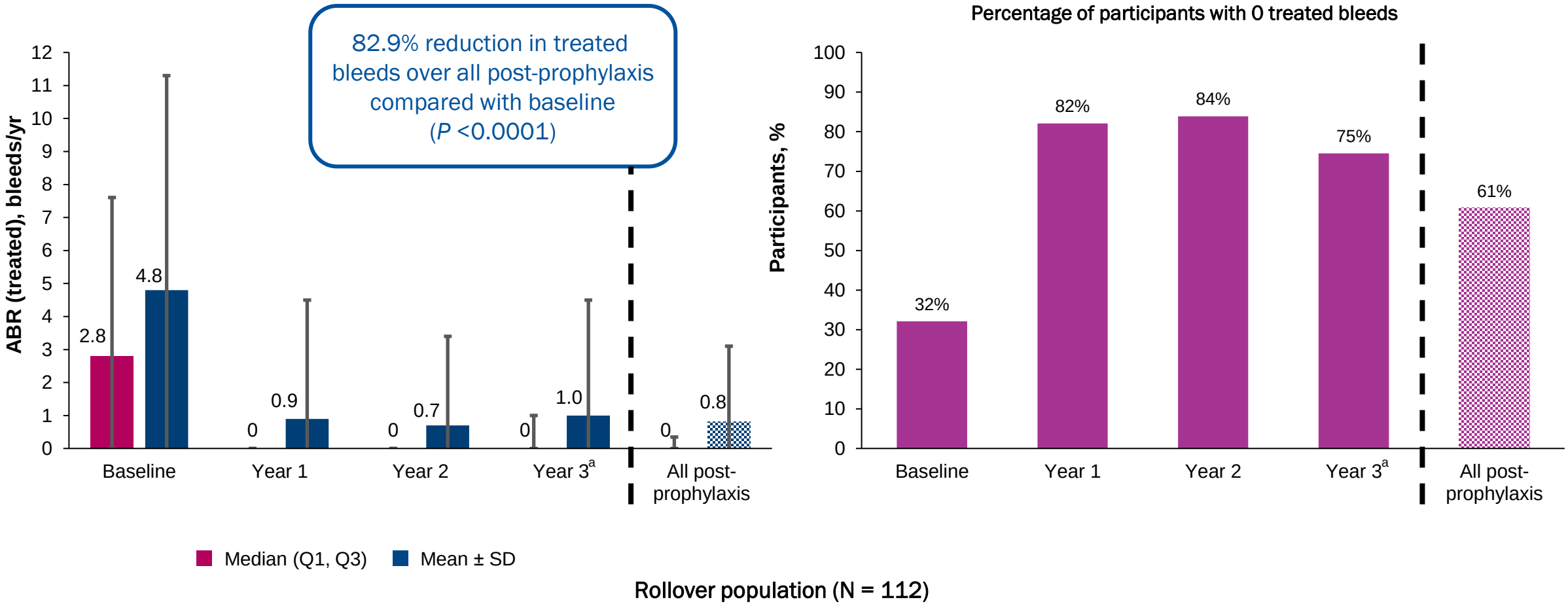
For participants who discontinued the study, missing FVIII values post-discontinuation were imputed to be 0 IU/dL through the data cutoff date for the analysis.
CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intent-to-treat; OSA, one-stage assay; SE, standard error; Q, quartile.

Participants by FVIII activity at the end of years 1, 2, and 3



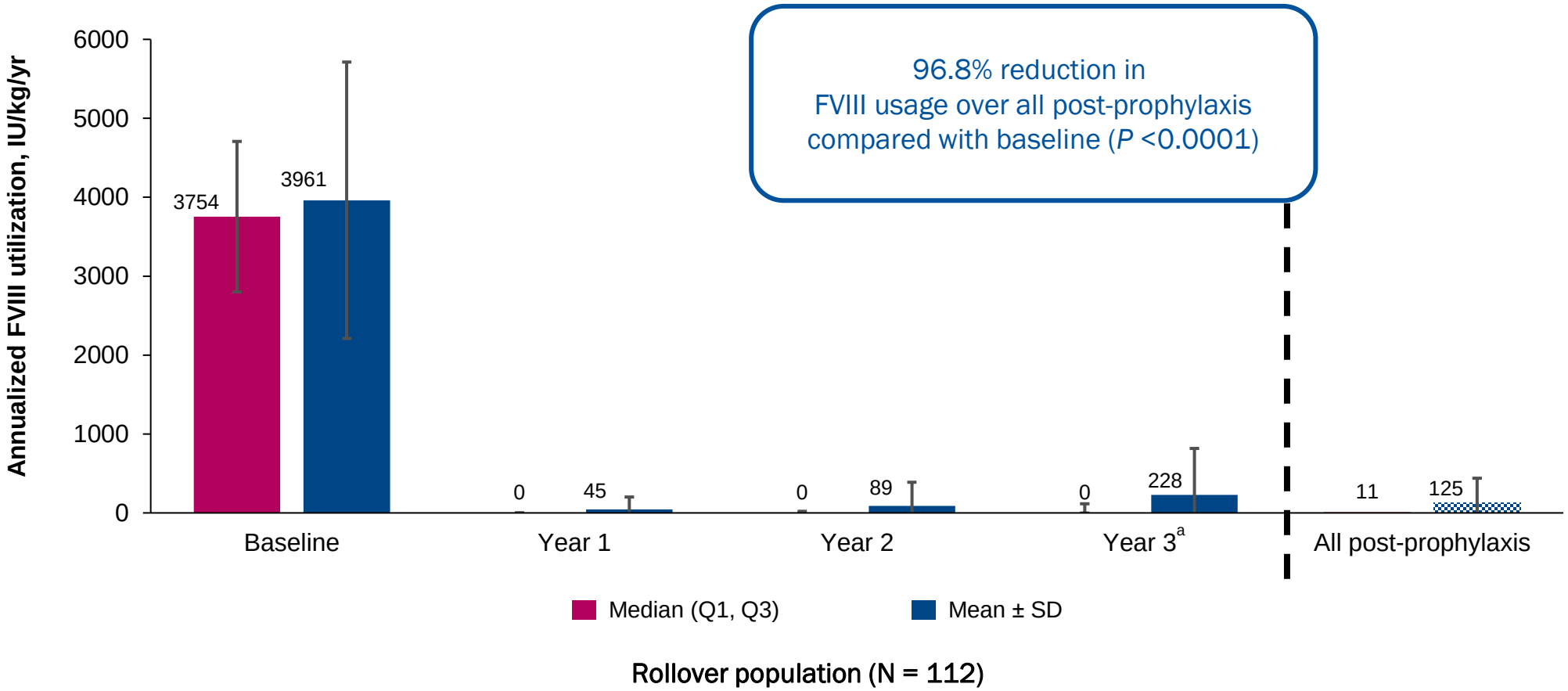
Values for participants who discontinued were imputed as 0.
FVIII, factor VIII; mITT, modified intent-to-treat.

Reduction in treated bleeds maintained over 3 years



Missing data were not imputed. [a]Year 3 data were based on N = 110 due to participants who discontinued from the study.
ABR, annualized bleeding rate; SD, standard deviation; Q, quartile.

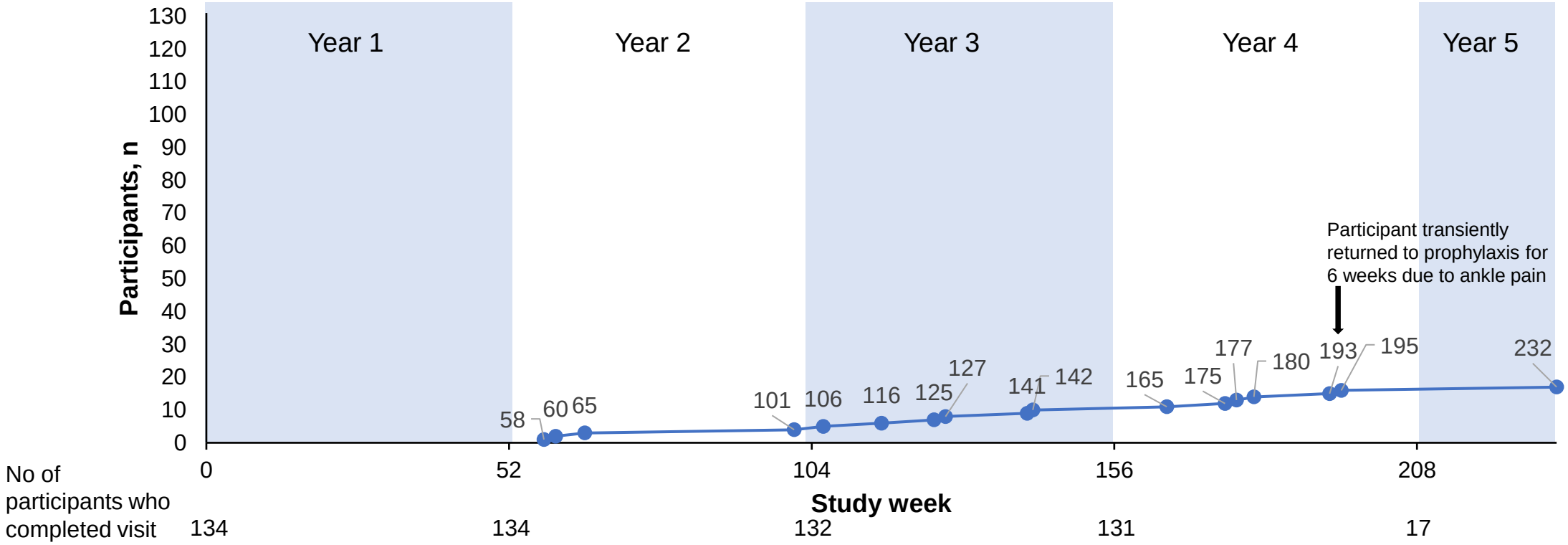
Reduction in FVIII utilization maintained over 3 years



Missing data were not imputed. [a]Year 3 data were based on N = 110 due to participants who discontinued from the study.
FVIII, factor VIII; Q, quartile; SD, standard deviation.

Participants who returned to prophylaxis

- To date, 17 participants returned to prophylaxis

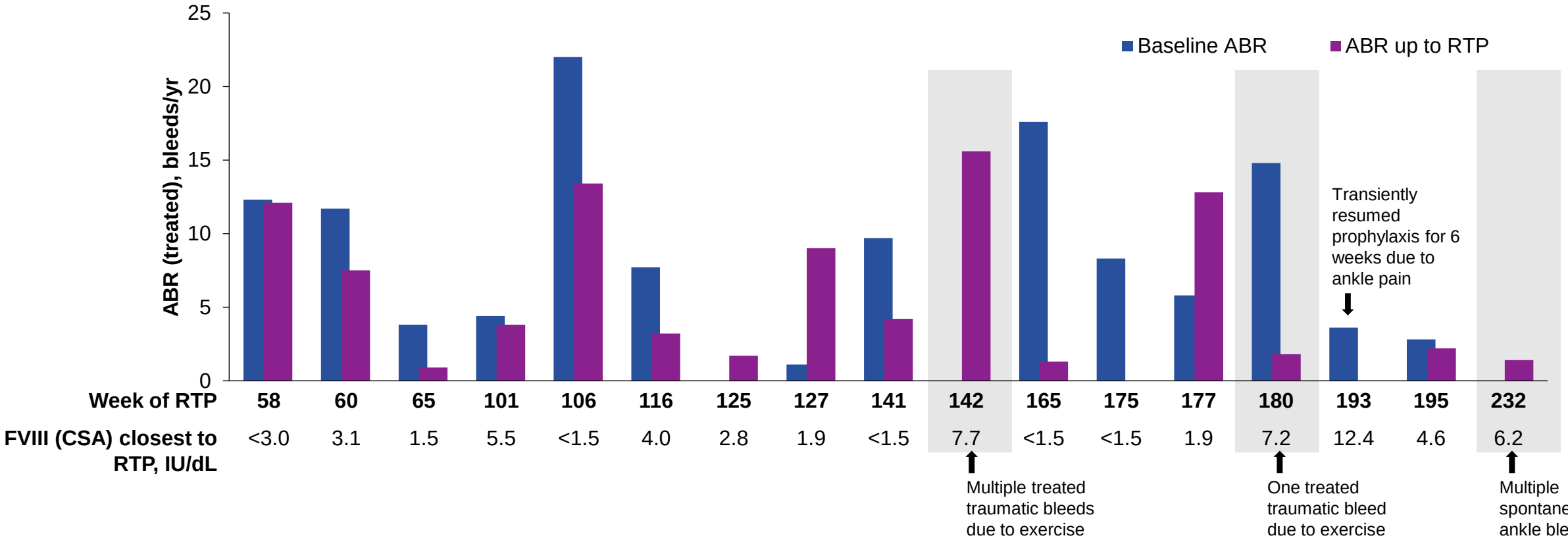


Participants who discontinued were not considered as returning to prophylaxis. Prophylaxis was defined as a FVIII infusion categorized as "usual FVIII prophylaxis" administered at least once a week for ≥4 consecutive weeks or ≥2 emicizumab injections in 1 month.

FVIII, factor VIII; ITT, intent-to-treat.

Participants who returned to prophylaxis

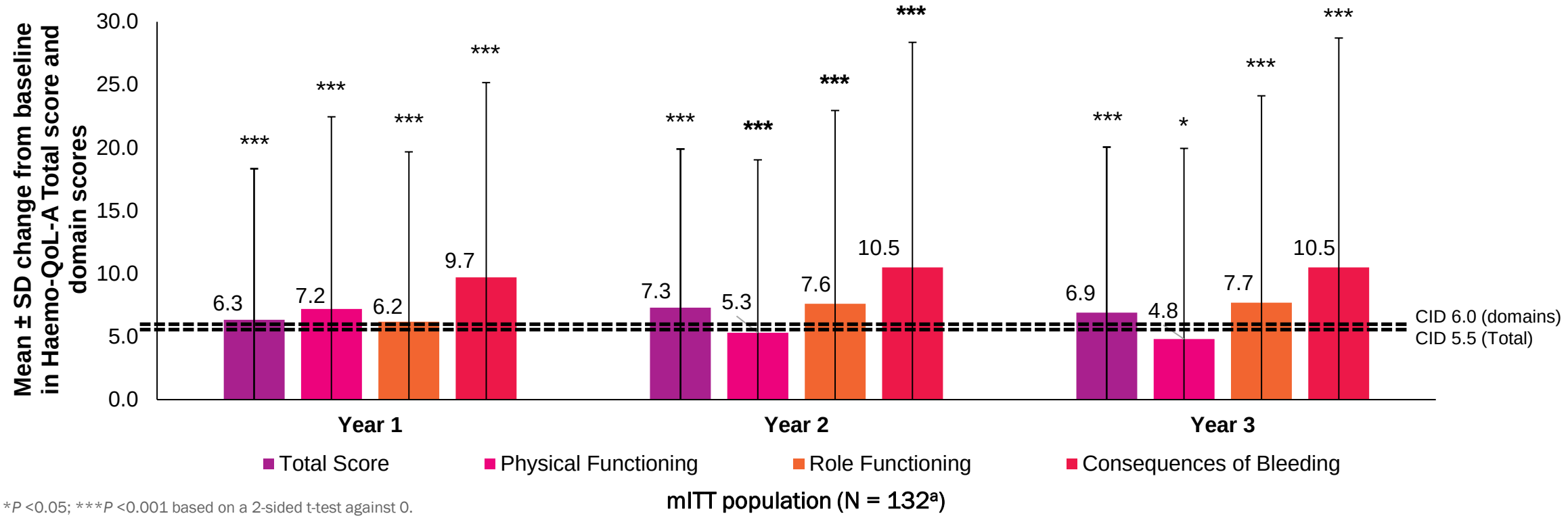
- Multifactorial decision influenced by ABR, FVIII, and individual preference



Prophylaxis was defined as a FVIII infusion categorized as "usual FVIII prophylaxis" administered at least once a week for ≥4 consecutive weeks or ≥2 emicizumab injections in one month.
ABR, annualized bleeding rate; CSA, chromogenic substrate assay; FVIII, factor VIII; ITT, intent-to-treat; RTP, return to prophylaxis.

Improvement in Haemo-QoL-A maintained at the end of year 3

- Change in mean Haemo-QoL-A Total Score from baseline to week 156 was 6.9
  - This exceeds the anchor-based CID of 5.5[1]



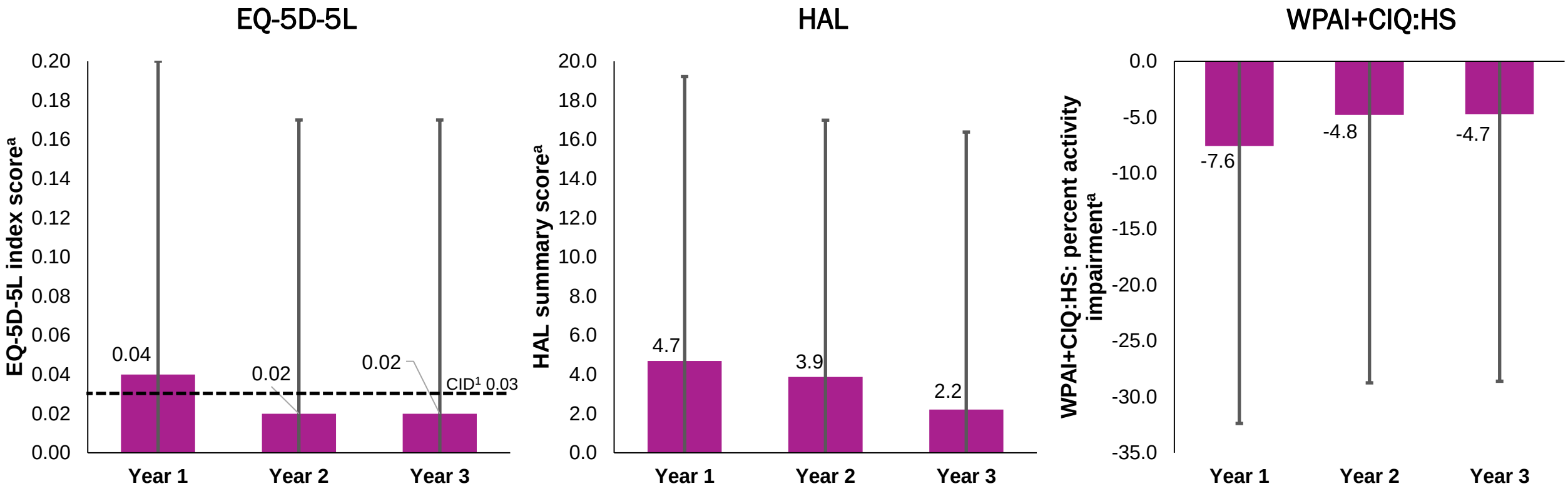
*P <0.05; ***P <0.001 based on a 2-sided t-test against 0.

[a]Change from baseline in Haemo-QoL-A Total Score and domain score results are based on available data at each time point, which may differ from the given N. Participants who resumed prophylaxis were excluded, and missing data were not imputed.

CID, clinically important difference; Haemo-QoL-A, Haemophilia-specific Quality of Life Questionnaire for Adults; mITT, modified intent-to-treat; SD, standard deviation.

1. Quinn J, et al. *Patient Relat Outcome Meas*. 2022;13:169-80.

Consistent change in HRQoL across different instruments



mITT population (N = 132[b])

[a]Mean ± SD change from baseline

[b]Change from baseline results are based on available data at each time point, which may differ from the given N value. Missing data were not imputed.

CID, clinically important difference; HAL, Hemophilia Activities List; HRQoL, health-related quality of life; mITT, modified intent-to-treat; SD, standard deviation; WPAI+CIQ:HS, Work Productivity and Activity Impairment Questionnaire + Classroom Impairment Questionnaire: Hemophilia Specific.

1. Kaplan RM. *COPD.* 2005;2(1):91-7.

Conclusions

- After 3 years of follow-up, the safety profile remains unchanged from previous reports
- Previously observed trends regarding change in FVIII activity were maintained
  - Among 17 participants dosed ≥4 years prior, year 4 values were similar to year 3
- A single infusion of valoctocogene roxaparvovec provided robust, durable hemostatic efficacy relative to FVIII prophylaxis over 3 years
  - 82.9% reduction in treated bleeds overall compared with baseline
  - 96.8% reduction in FVIII usage overall compared with baseline
- To date, 17 of 134 participants returned to prophylaxis: 10 between years 1 and 3, and 7 after year 3
  - The decision to return to prophylaxis appears to be multifactorial and influenced by factors such as FVIII activity level, bleeds, desired physical activity level, and personal preferences
- Significant, meaningful improvements in QoL were maintained at the end of year 3

FVIII, factor VIII; QoL, quality of life.

Acknowledgments

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