Efficacy and safety of valoctocogene roxaparvovec 4 years after gene transfer in GENEr8-1

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International Society on Thrombosis and Haemostasis 2024

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Disclosures

- I have participated in advisory boards for BioMarin Pharmaceutical Inc., CSL, Pfizer, Sanofi, and Sobi

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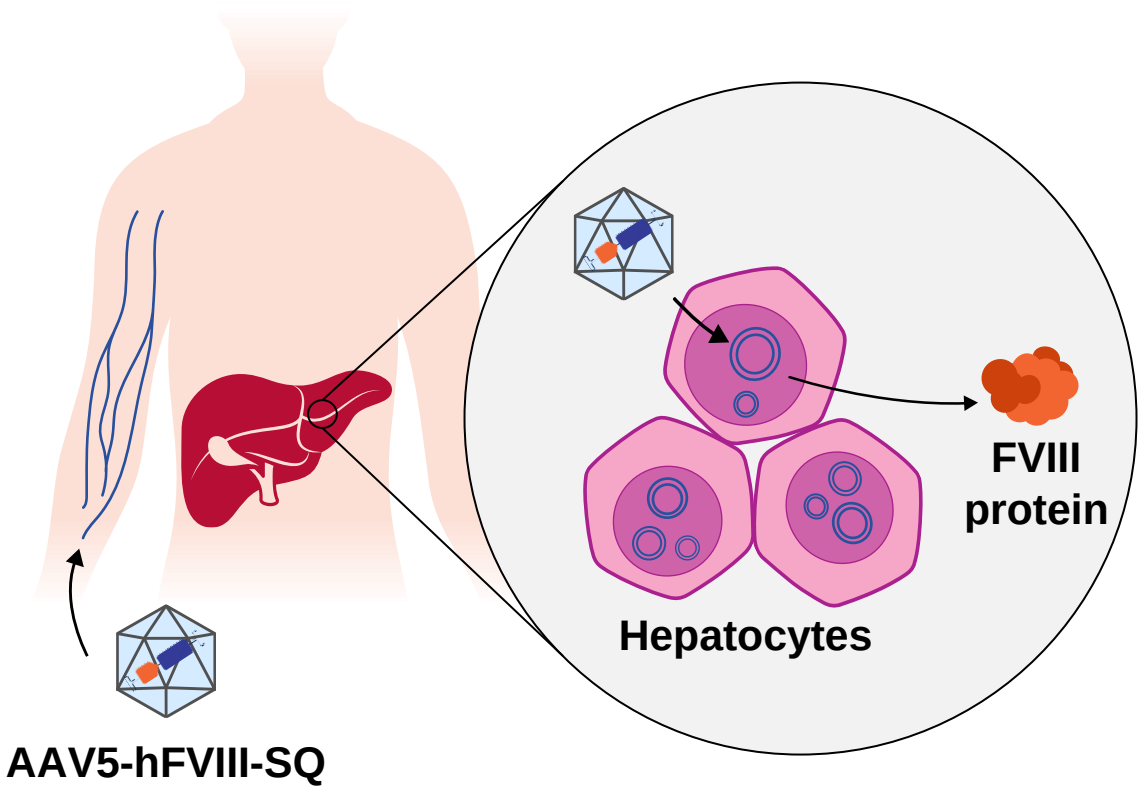
Valoctocogene roxaparvovec for severe hemophilia A

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a B-domain-deleted FVIII coding sequence to enable FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1,2]

In the open-label, phase 3 GENEr8-1 trial, participants who received $6x10^{13}$ vg/kg valoctocogene roxaparvovec had improved protection from bleeds compared with regular FVIII prophylaxis over 3 years[1,2]

4

Here, we evaluate efficacy and safety outcomes 4 years after treatment



1. Ozelo M, et al. *N Engl J Med.* 2022;386(11):1013-25. 2. Mahlangu J, et al. *N Engl J Med.* 2023;388:694-705.
AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant.

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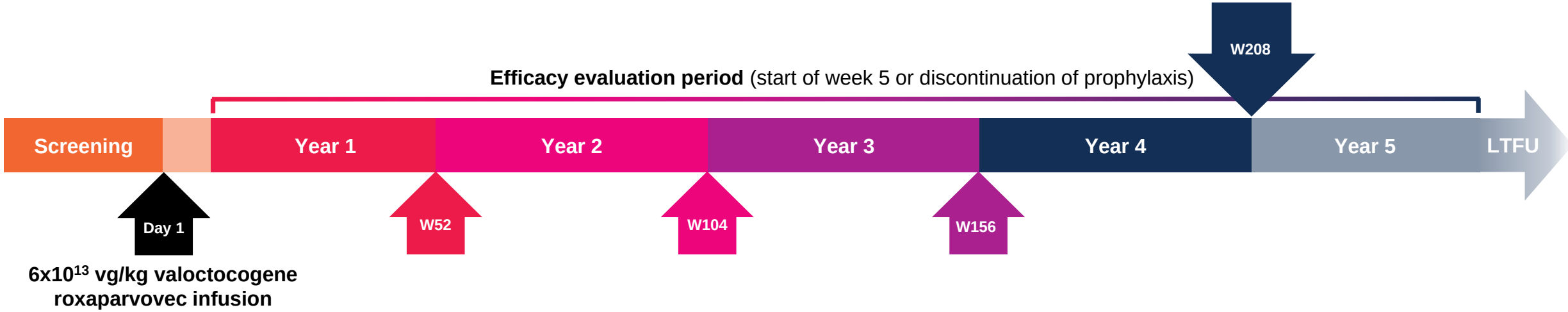
Study design

Eligibility

- 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, fibrosis, or cirrhosis

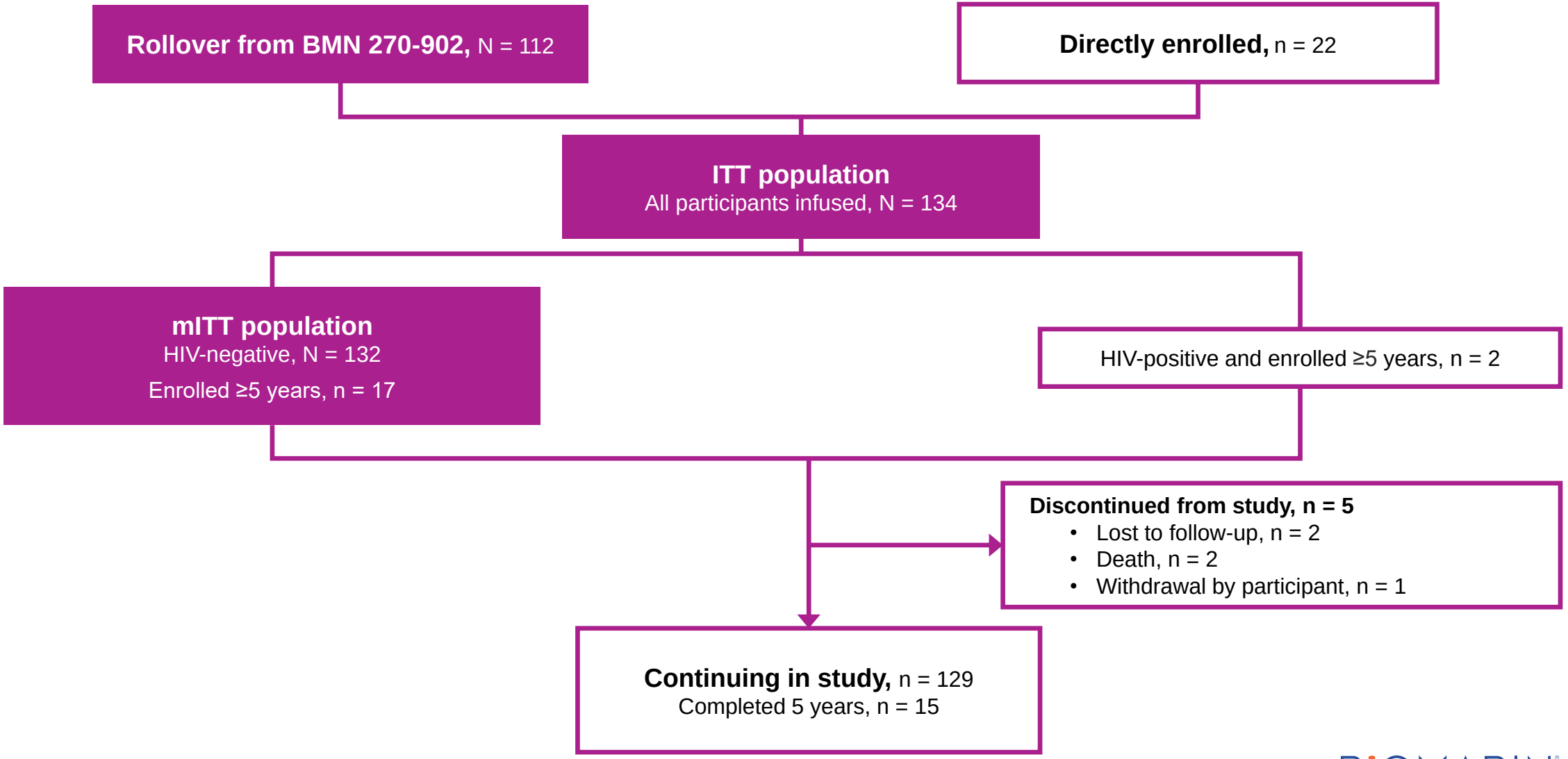
Endpoints

- FVIII activity
- Change from baseline
  - Annualized bleeding rate
  - Annualized FVIII infusion rate
  - HRQOL (covered in a separate presentation)
- Safety



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; HRQOL, health-related quality of life; LTFU, long-term follow-up; W, week.

Participant disposition



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

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Baseline characteristics

Baseline characteristics	Rollover population N = 112	mITT N = 132	ITT N = 134
Age, years, mean (range)	31.8 (19–70)	31.4 (18–70)	31.7 (18–70)
Race, n (%)			
White	78 (69.6)	94 (71.2)	96 (71.6)
Asian	17 (15.2)	19 (14.4)	19 (14.2)
Black or African American	14 (12.5)	15 (11.4)	15 (11.2)
Hawaiian or Pacific Islander	1 (0.9)	1 (0.8)	1 (0.7)
Not provided	2 (1.8)	3 (2.3)	3 (2.2)
Hispanic or Latino ethnicity, n (%)	5 (4.5)	7 (5.3)	7 (5.2)
BMI, kg/m^2, mean ± SD	25.2 ± 4.7	25.3 ± 4.6	25.3 ± 4.6
Medical history, n (%)			
Hepatitis B	17 (15.2)	18 (13.6)	20 (14.9)
Hepatitis C	33 (29.5)	39 (29.5)	41 (30.6)
HIV	0	0	2 (1.5)
Number of problem joints,[a] n (%)			
0	82 (73.2)	95 (72.0)	97 (72.4)
1	13 (11.6)	17 (12.9)	17 (12.7)
2	9 (8.0)	9 (6.8)	9 (6.7)
3	6 (5.4)	8 (6.1)	8 (6.0)
>3	2 (1.8)	3 (2.3)	3 (2.2)

[a]Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.
BMI, body mass index; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified ITT; SD, standard deviation.

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No new safety signals in year 4

ITT population

In year 4

No new safety signals

- Low-grade, transient ALT elevations remained the most common AE in year 4

No treatment-related SAEs occurred

No new malignancies

As of the cutoff date

No FVIII inhibitors were observed

No thromboembolic events occurred

Participants, n (%)		Year 1 (N = 134)	Year 2 (N = 134)	Year 3 (N = 131)	Year 4 (N = 131)	All follow-up
AEs		134 (100.0)	113 (84.3)	105 (80.2)	106 (80.9)	134 (100.0)
SAEs		21 (15.7)	6 (4.5)	9 (6.9)	13 (9.9)	37 (27.6)
Treatment-related AEs[a]		123 (91.8)	28 (20.9)	15 (11.5)	10 (7.6)	123 (91.8)
Glucocorticoid-related AEs[a]		80 (59.7)	10 (7.5)	1 (0.8)	1 (0.8)	81 (60.4)
AEs of special interest	ALT elevation	114 (85.1)	40 (29.9)	31 (23.7)	56 (42.7)	121 (90.3)
	ALT elevation ≥grade 3	11 (8.2)	1 (0.7)	0	1 (0.8)[b]	12 (9.0)
	Potential Hy's law case	0	0	0	0	0
	Infusion-related reactions[c]	12 (9.0)	0	0	0	12 (9.0)
	Systemic hypersensitivity	7 (5.2)	0	0	0	7 (5.2)
	Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	0	3 (2.2)
	Thromboembolic events	0	0	0	0	0
	Anti-FVIII neutralizing antibodies	0	0	0	0	0
	Malignancy (except nonmelanoma skin cancer)	0	0	1 (0.8)	0	1 (0.7)

[a]Treatment-related and glucocorticoid-related AEs were assessed by the investigator.
[b]This event was downgraded after the data cutoff (November 15, 2023).
[c]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, intention-to-treat; SAE, serious AE.

ALT elevation and glucocorticoid use

ITT population

In year 4

56 (42.7%) participants experienced an ALT elevation, most of which were low-grade and transient

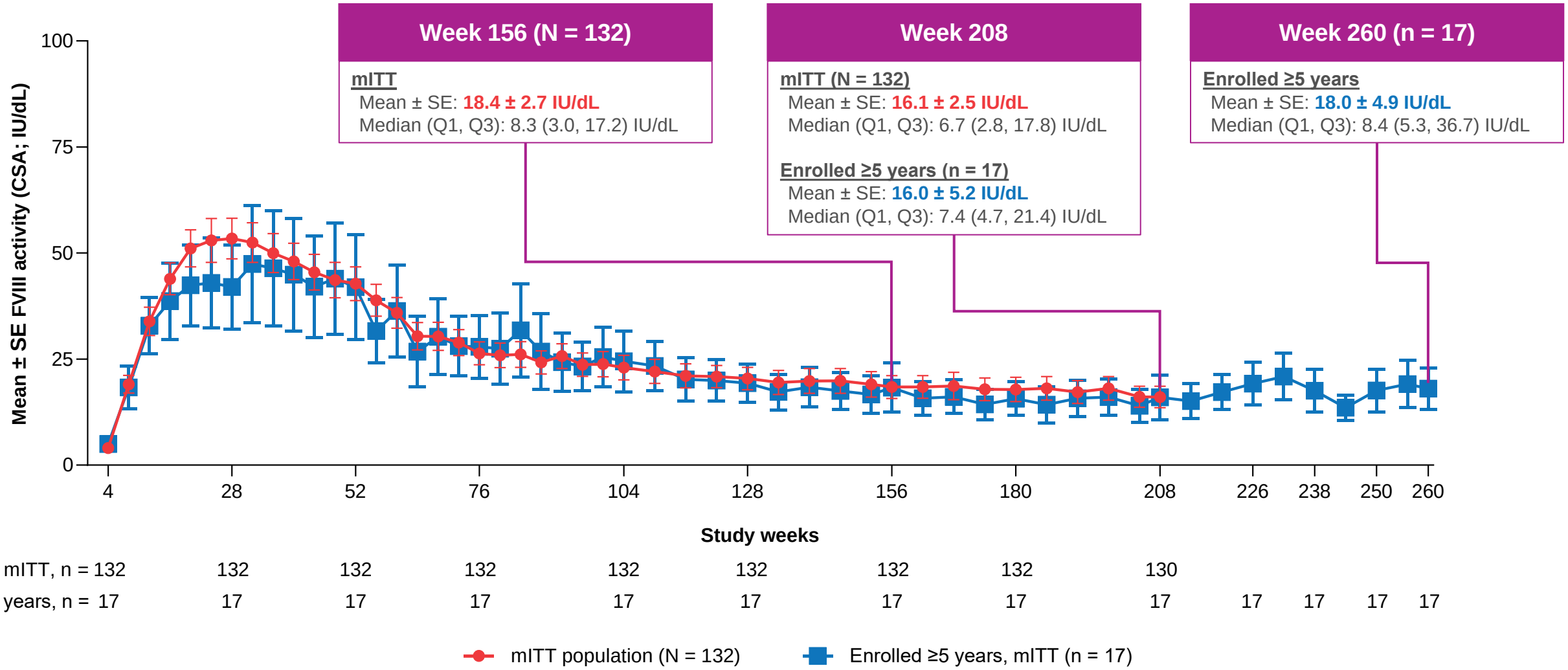
No participants initiated glucocorticoids to manage ALT elevations after week 84

During year 4	With AEs in year 4 (N = 131)
ALT elevation >ULN, n (%)	21 (16.0)
ALT elevation >1.5x baseline, n (%)	55 (42.0)
Used glucocorticoids for any purpose, n (%)	3 (2.3)
Total duration, weeks, median (range)	1.4 (1.0–12.1)
Total dose, mg, median (range)	200.0 (200–1475)
Used glucocorticoids for ALT elevation, n (%)	0 (0.0)
Total duration, weeks, median (range)	NA
Total dose, mg, median (range)	NA

[a]Participant initiated use for ALT elevation at the start of year 2 and continues use despite return to normal ALT levels prior to year 3.
AE, adverse event; ALT, alanine aminotransferase; ITT, intention-to-treat; NA, not applicable; ULN, upper limit of normal.

FVIII activity (chromogenic) maintained between years 3 and 4

mITT population



Because 2 participants did not reach year 4 follow-up, week 208 data are based on 130 participants. For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.

CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intention-to-treat; Q, quartile; SE, standard error.

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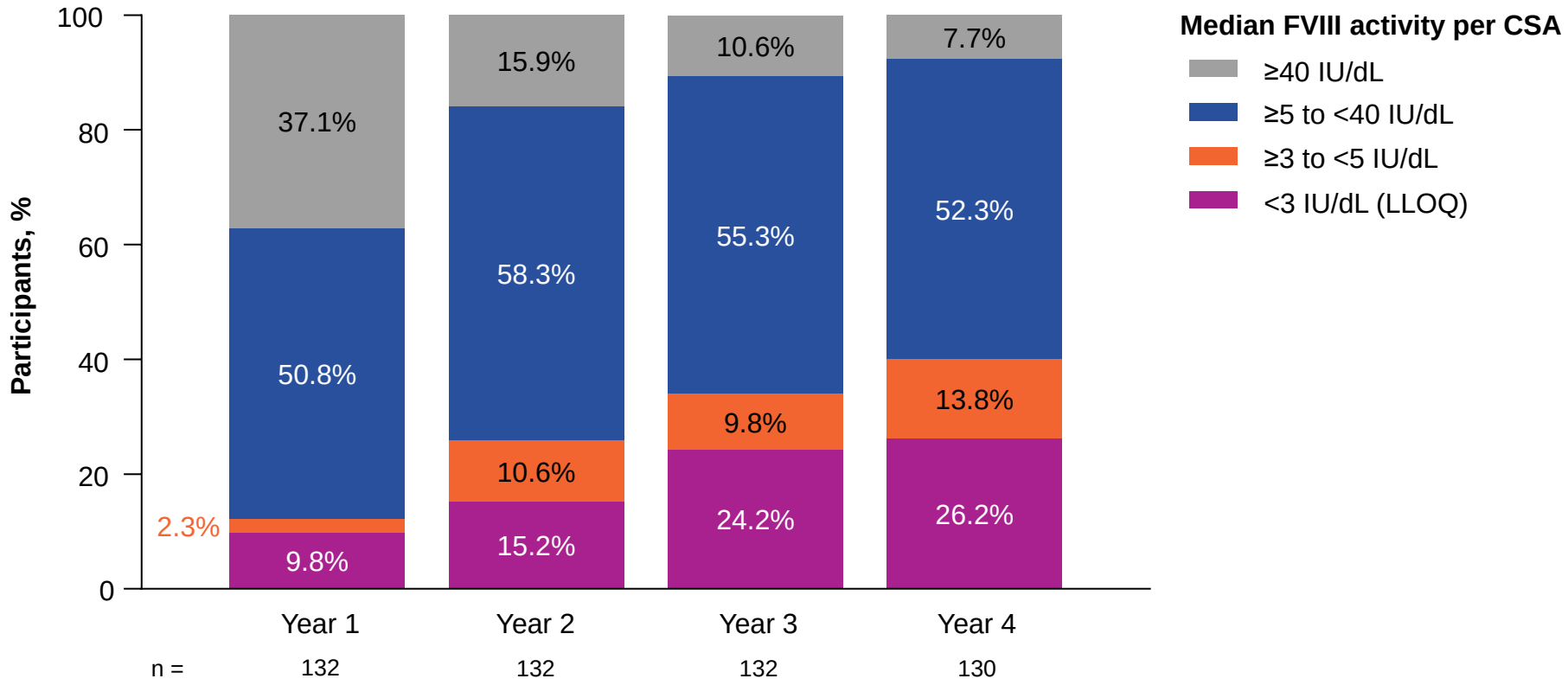
FVIII activity (chromogenic) ranges at the end of year 4

mITT population

Most participants remain in the mild hemophilia range



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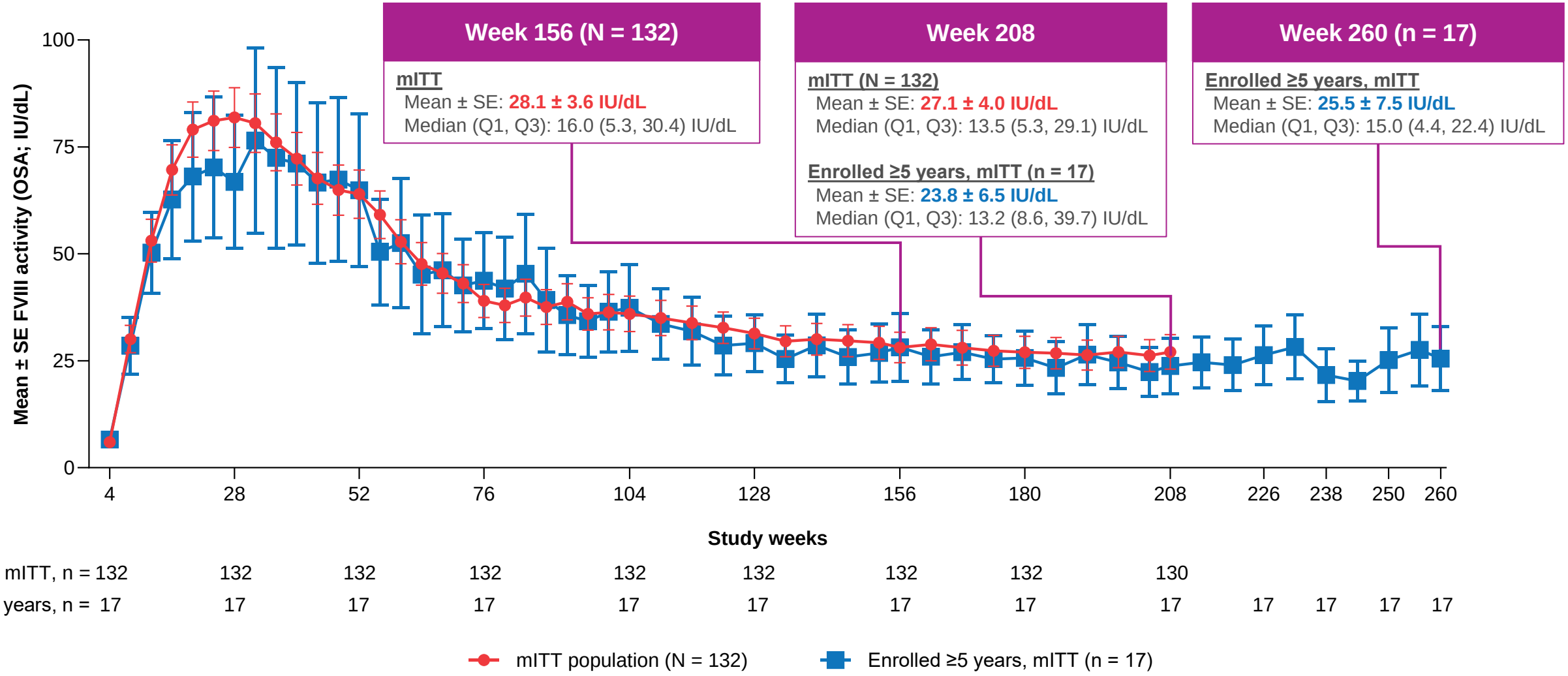
CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intention-to-treat.

FVIII activity (one-stage) maintained between years 3 and 4

mITT population



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FVIII, factor VIII; mITT, modified intention-to-treat; OSA, one-stage assay; Q, quartile; SE, standard error.

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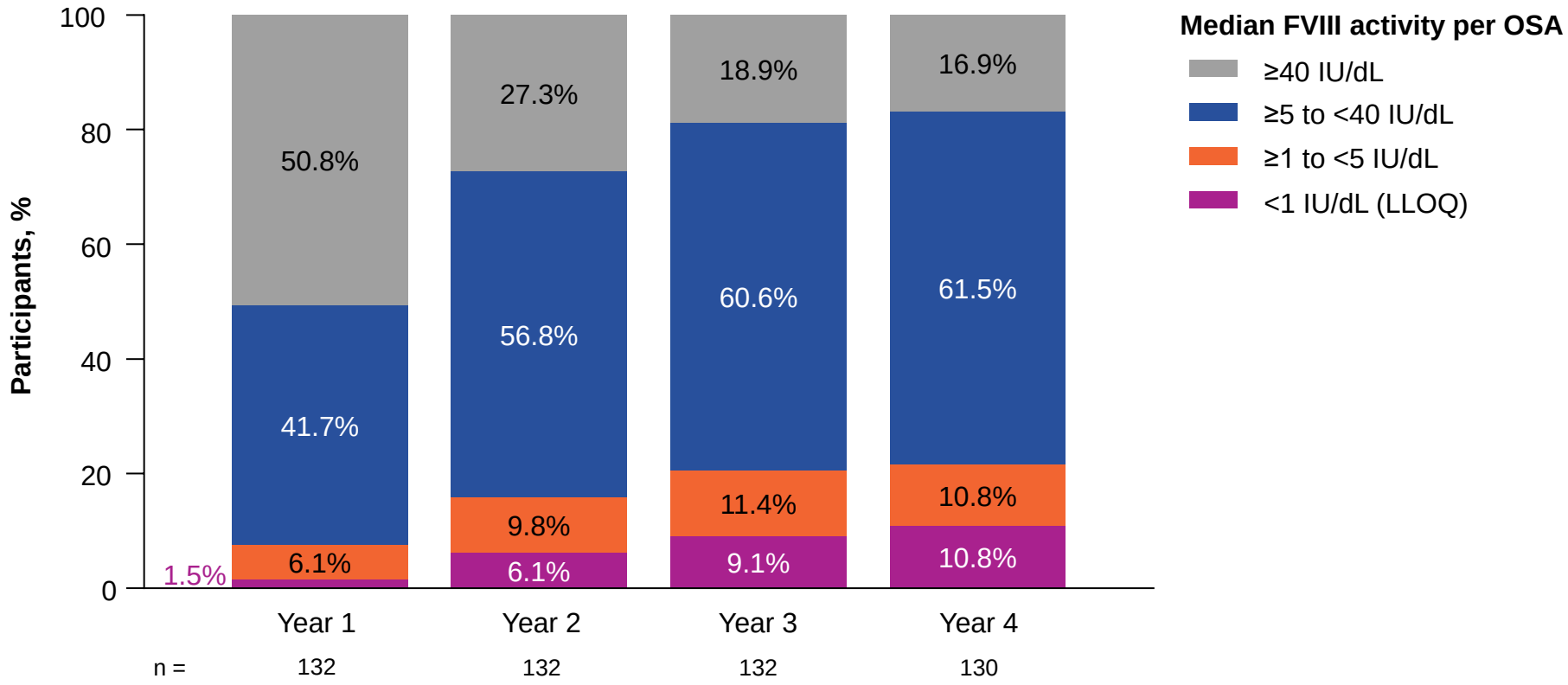
FVIII activity (one-stage) ranges at the end of year 4

mITT population

Most participants remain in the mild hemophilia range



Because 2 participants did not reach year 4 follow-up, week 208 data are based on 130 participants. For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.

FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intention-to-treat; OSA, one-stage assay.

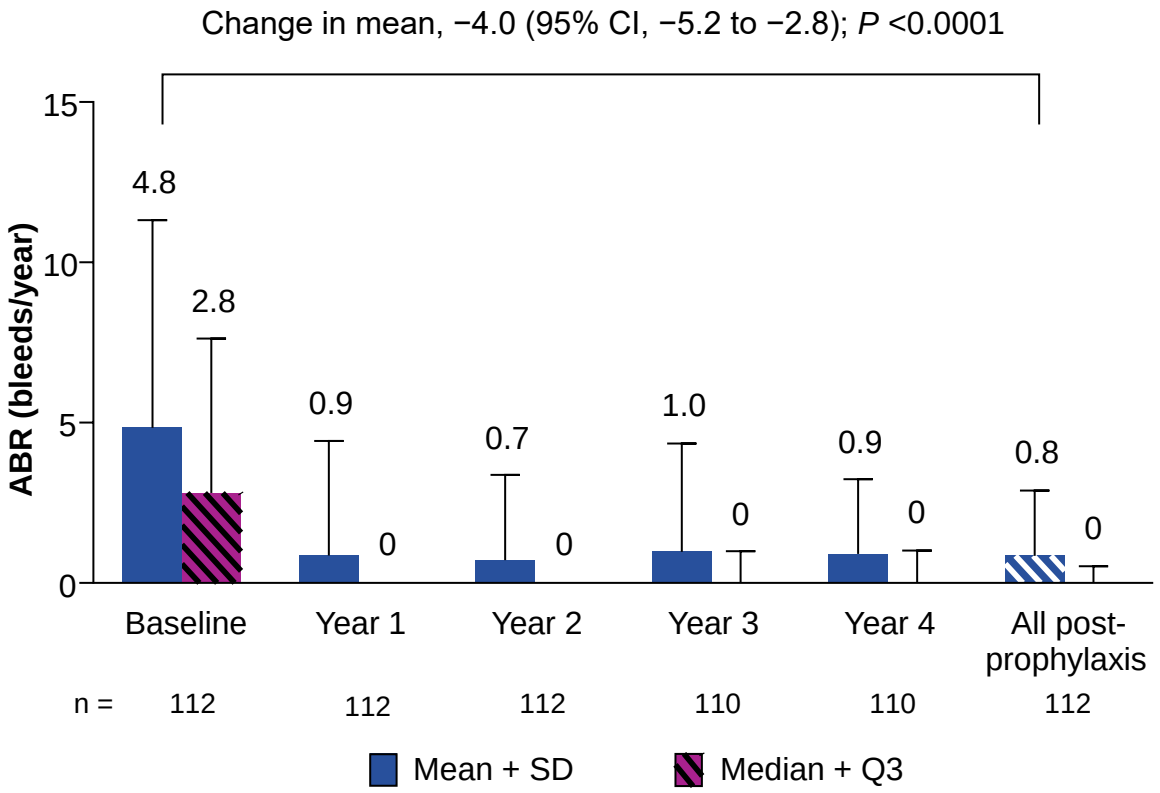
Reduction in treated bleeds maintained over 4 years

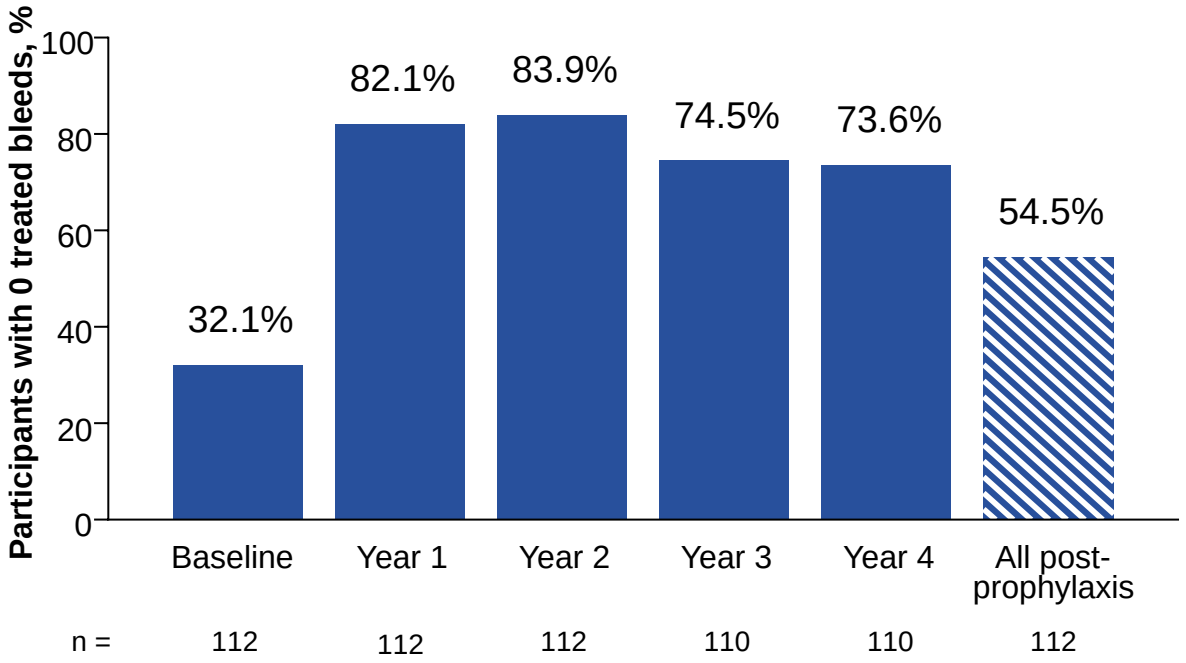
Rollover population

ABR for treated bleeds decreased >80% from baseline during the post-prophylaxis period

In year 4, >70% of participants had no treated bleeds

82.6% reduction





Missing data were not imputed.
ABR, annualized bleeding rate; CI, confidence interval; Q, quartile; SD, standard deviation.

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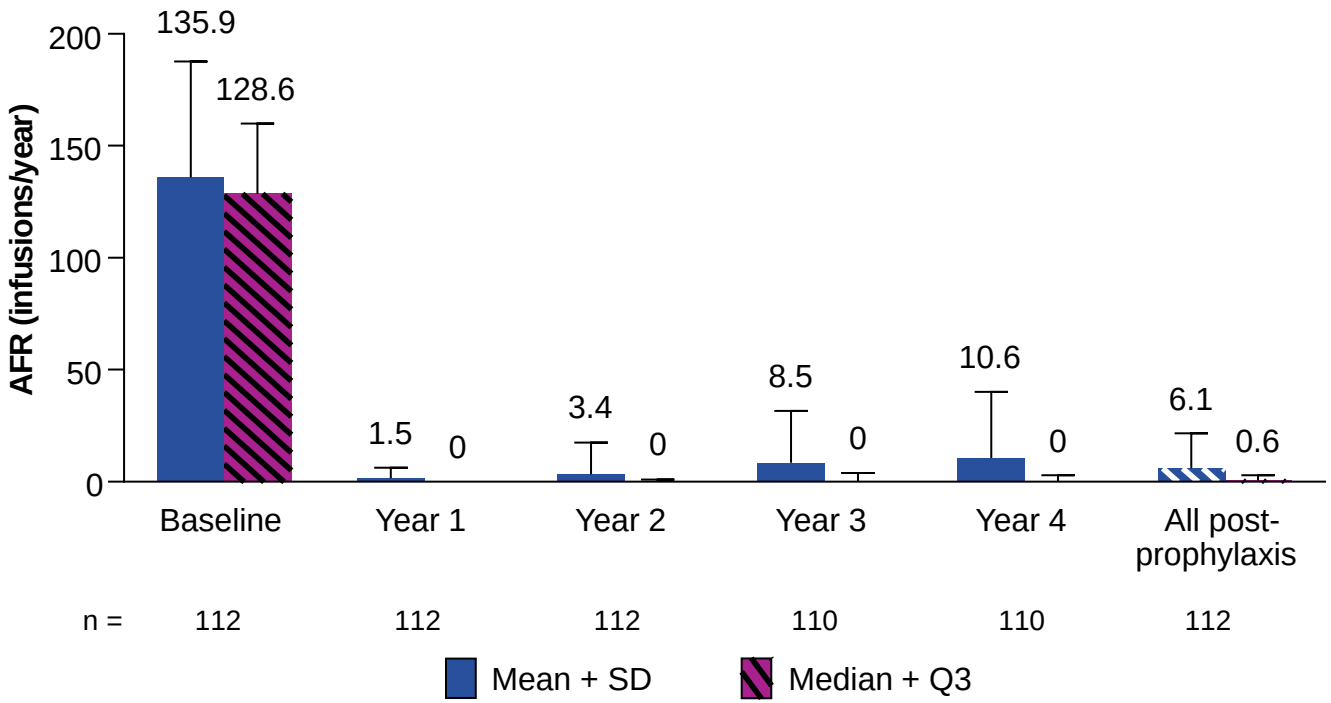
Reduction of FVIII infusion rate maintained through year 4

Rollover population

Annualized FVIII infusion rate decreased >95% from baseline during the post-prophylaxis period

95.5% reduction

Change in mean, −129.8 (95% CI, −139.4 to −120.1); *P* <0.0001



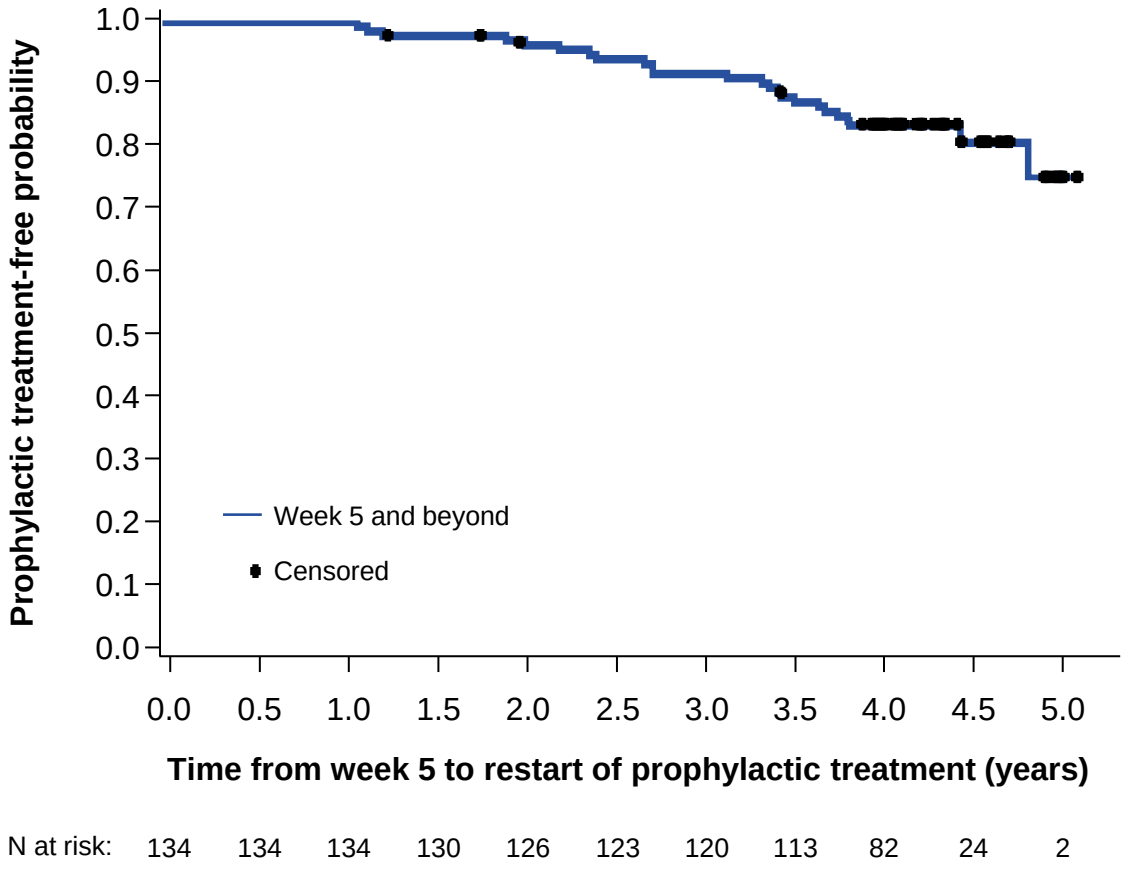
Missing data were not imputed.

AFR, annualized FVIII infusion rate; CI, confidence interval; HA, hemophilia A; FVIII, factor VIII; Q, quartile; SD, standard deviation.

Most participants remain off prophylaxis

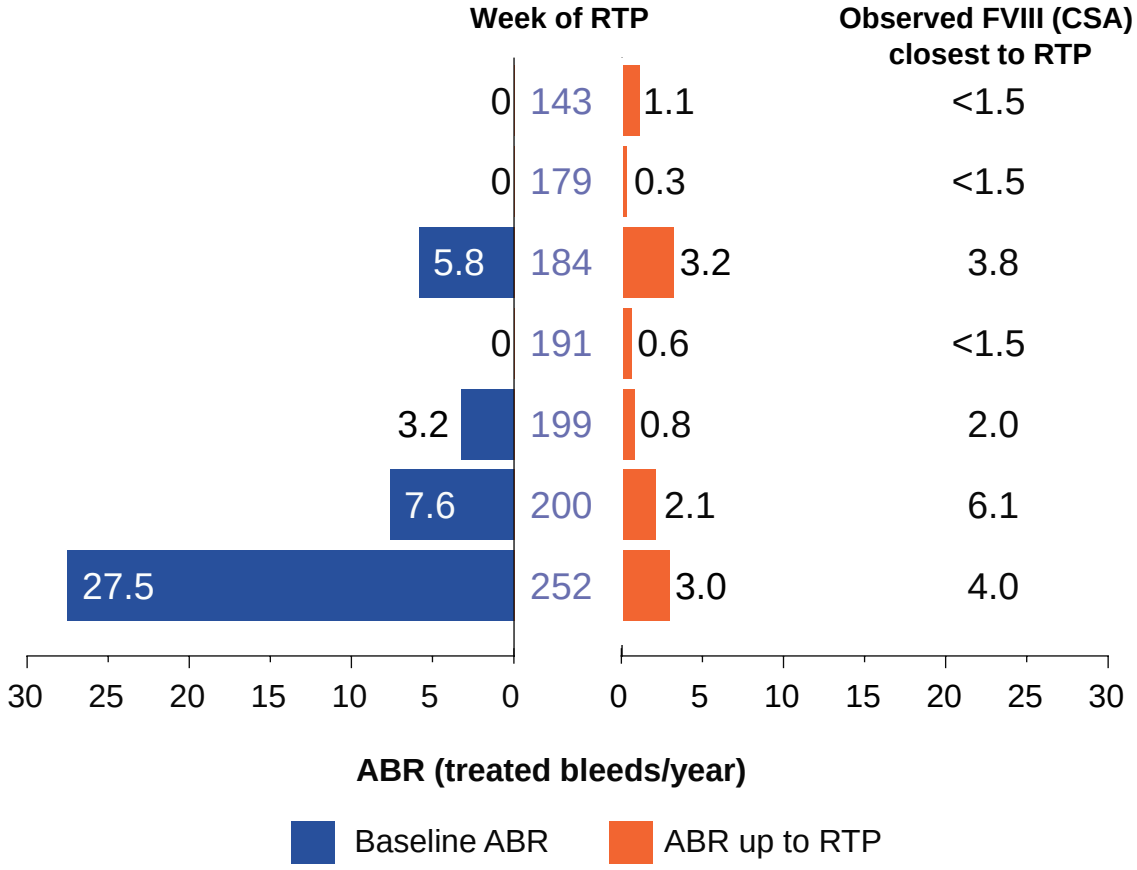
ITT population

Overall, 24 participants resumed prophylaxis



N at risk:	134	134	134	130	126	123	120	113	82	24	2

Since the previous data cutoff, 7 additional participants resumed prophylaxis



Missing data were not imputed.

ABR, annualized bleeding rate; CSA, chromogenic substrate assay; FVIII, factor VIII; ITT, intention-to-treat; RTP, return to prophylaxis.

Conclusions

A single infusion of valoctocogene roxaparvovec provides durable bleeding protection for 4 years with an acceptable safety profile

No new safety signals

- ALT elevation remained the most common AE in year 4; none have required glucocorticoid use since year 2
- No FVIII inhibitors or thromboembolic events

FVIII activity was maintained

- FVIII activity remained in the mild hemophilia range
- Slope of decline in FVIII activity continues to approach 0
- Among the 17 participants dosed ≥5 years prior, year 5 values were similar to year 4

Durable hemostatic efficacy

- Rate of treated bleeds in the post-prophylaxis period remains decreased >80% from baseline
- Most participants had no treated bleeds during year 4

Most participants remain off prophylaxis

- Decisions to RTP were individual and part of a shared decision-making process that considered multiple factors

AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; RTP, return to prophylaxis.

Acknowledgments

- **Thank you to all trial participants, their families, study-site personnel, and investigators**
- Funding for this study was provided by BioMarin Pharmaceutical Inc.
- Medical writing support was provided by Amin Ghane, PhD, of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc.

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