Safety and efficacy of valoctocogene roxaparvovec gene transfer for severe hemophilia A: an update from 4 years after treatment

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Disclosures

- I have served on advisory boards and speakers bureaus or as a consultant for Bayer, BioMarin Pharmaceutical Inc., CSL Behring, Genentech, Novo Nordisk, Octapharma, Sanofi, and Takeda

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Valoctocogene roxaparvovec for severe hemophilia A

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a 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]

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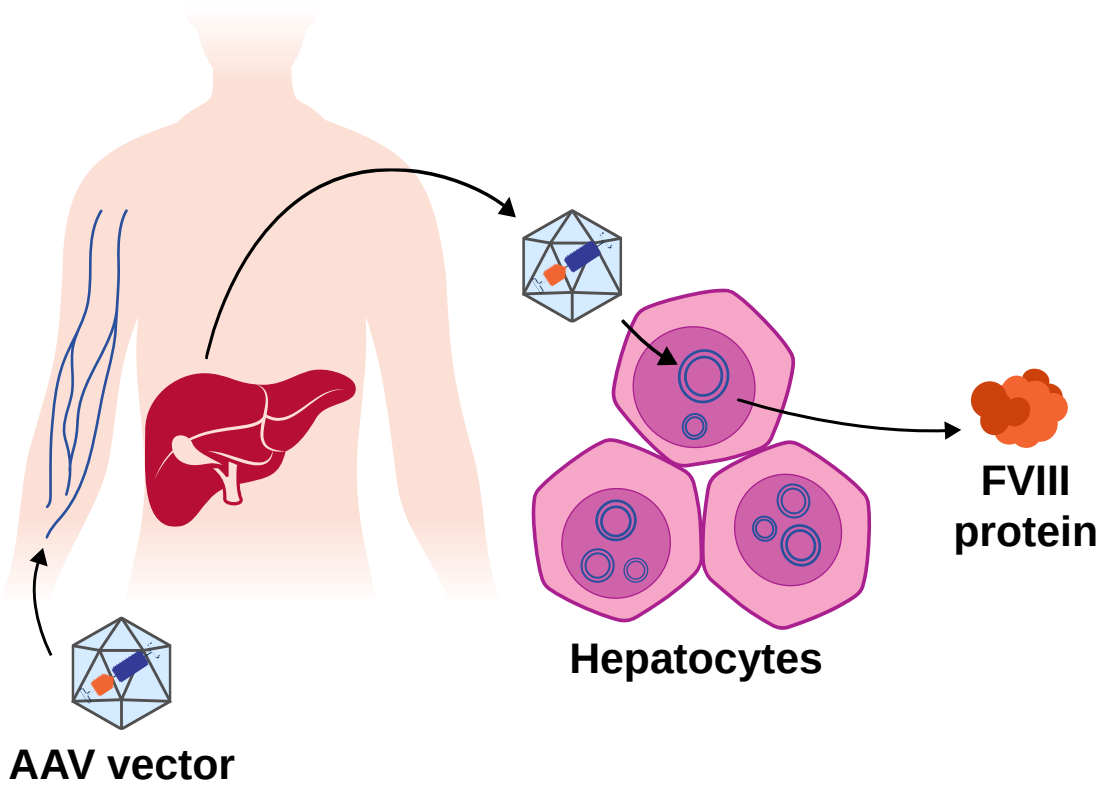
Here, we present outcomes 4 years after gene transfer



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.
AAV, adeno-associated virus; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant.

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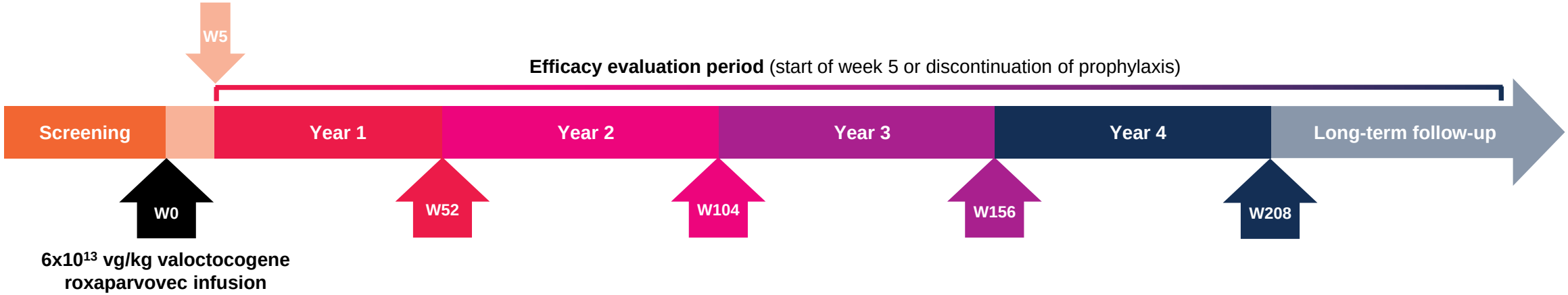
Study design

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

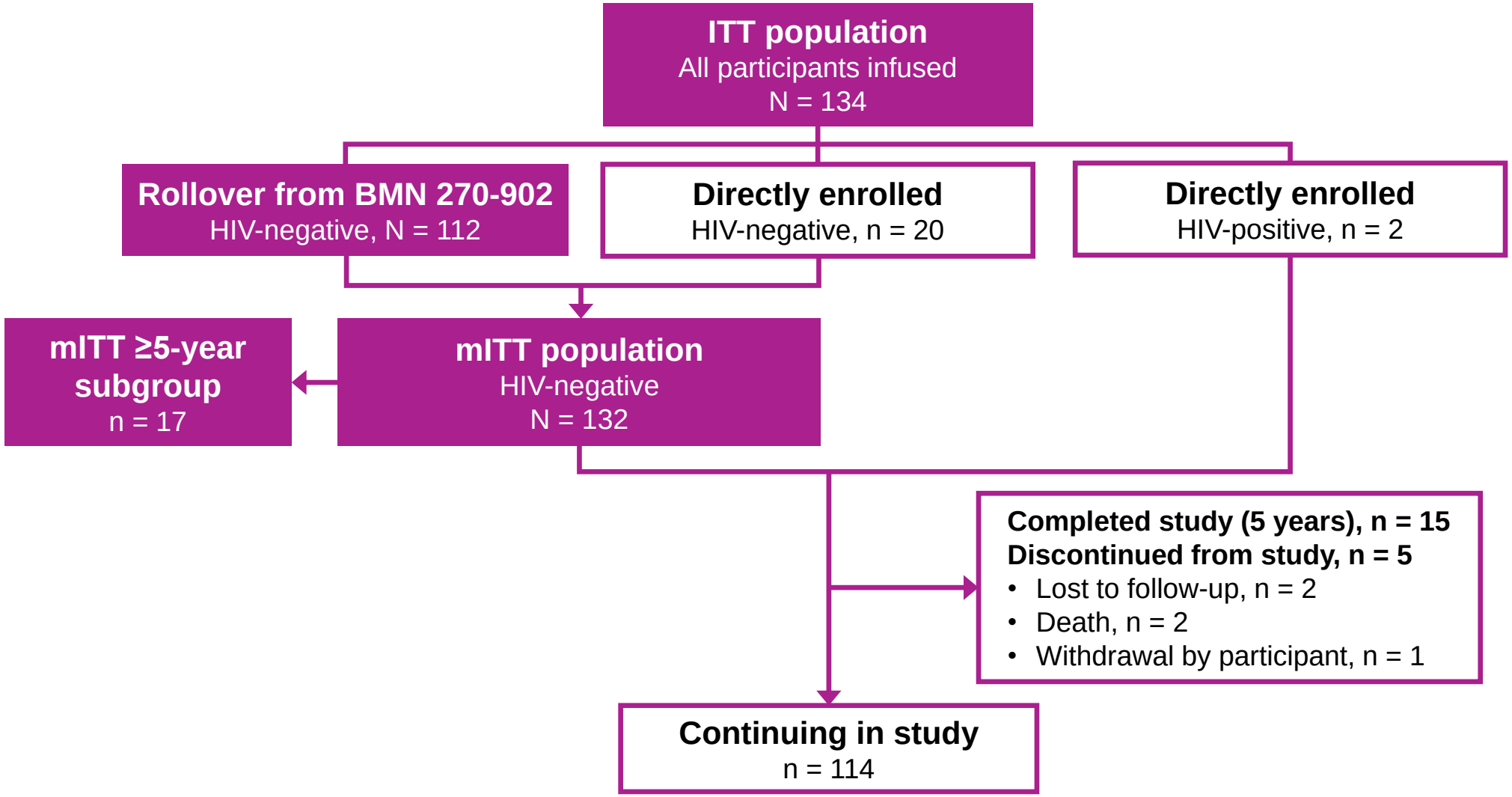
Endpoints

- FVIII activity
- Change from baseline during post-prophylaxis
  - Annualized bleeding rate
  - Annualized FVIII infusion rate
  - HRQOL
- Safety



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

Participant disposition



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

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Baseline characteristics

Baseline characteristics	Rollover population N = 112	mITT N = 132	ITT N = 134
Age, years, mean ± SD	31.8 ± 10.6	31.4 ± 10.1	31.7 ± 10.3
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, intent-to-treat; mITT, modified intent-to-treat; SD, standard deviation.

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No new safety signals in year 4

ITT population

In year 4:

No new safety signals

- ALT elevations remained the most common AE in year 4

No treatment-related SAEs occurred

No malignancies occurred in year 4

As of the cutoff date:

No FVIII inhibitors were observed

No thromboembolic events occurred

Participants, n (%)		With AEs in year 4 (N = 131)
AEs		106 (80.9)
SAEs		13 (9.9)
Treatment-related AEs[a]		10 (7.6)
Glucocorticoid-related AEs		1 (0.8)
AEs of special interest	ALT elevation	56 (42.7)
	ALT elevation ≥ grade 3	1 (0.8)[b]
	Potential Hy's law case	0
	Infusion-related reactions[c]	0
	Systemic hypersensitivity	0
	Anaphylactic or anaphylactoid reactions	0
	Thromboembolic events	0
	Anti-FVIII neutralizing antibodies	0
	Malignancy (except non-melanoma skin cancer)	0

[a]Treatment-related and glucocorticoid-related AEs were assessed by the investigator.
[b]This event was downgraded after the data cutoff.
[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, intent-to-treat; SAE, serious AE.

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ALT elevation and corticosteroid use

ITT population

In year 4:

4

56 (42.7%) participants had an ALT elevation

No participants used glucocorticoids to manage ALT elevations

Since year 2, no participants used glucocorticoids to manage ALT elevations

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 corticosteroids for any purpose, n (%)	3 (2.3)
Total duration, weeks, median (min, max)	1.4 (1.0, 12.1)
Total dose, mg, median (min, max)	200.0 (200, 1475)
Used corticosteroids for ALT elevation, n (%)	0 (0.0)
Total duration, weeks, median (min, max)	NA
Total dose, mg, median (min, max)	NA

AE, adverse event; ALT, alanine aminotransferase; ITT, intent-to-treat; max, maximum; min, minimum; NA, not applicable; ULN, upper limit of normal.

FVIII activity between years 3 and 4

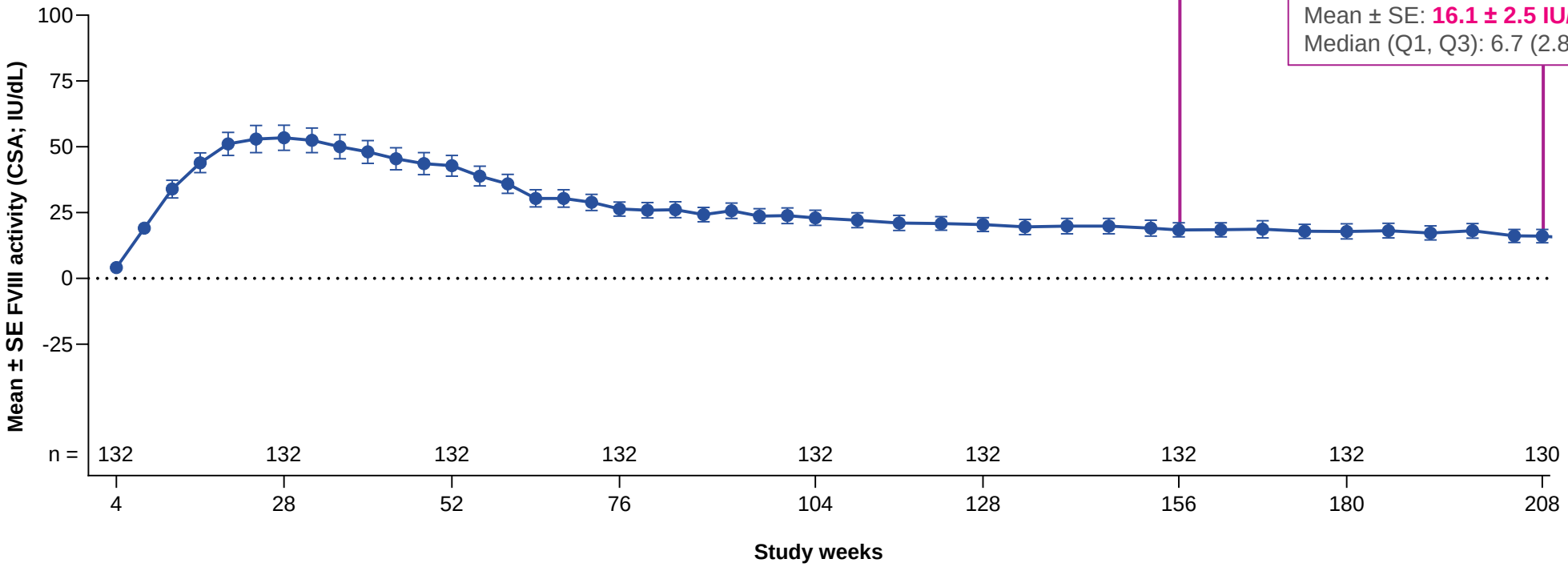
mITT population *(chromogenic substrate assay)*

Week 156

Mean ± SE: 18.4 ± 2.7 IU/dL
Median (Q1, Q3): 8.3 (3.0, 17.2) IU/dL

Week 208

Mean ± SE: **16.1 ± 2.5 IU/dL**
Median (Q1, Q3): 6.7 (2.8, 17.8) IU/dL



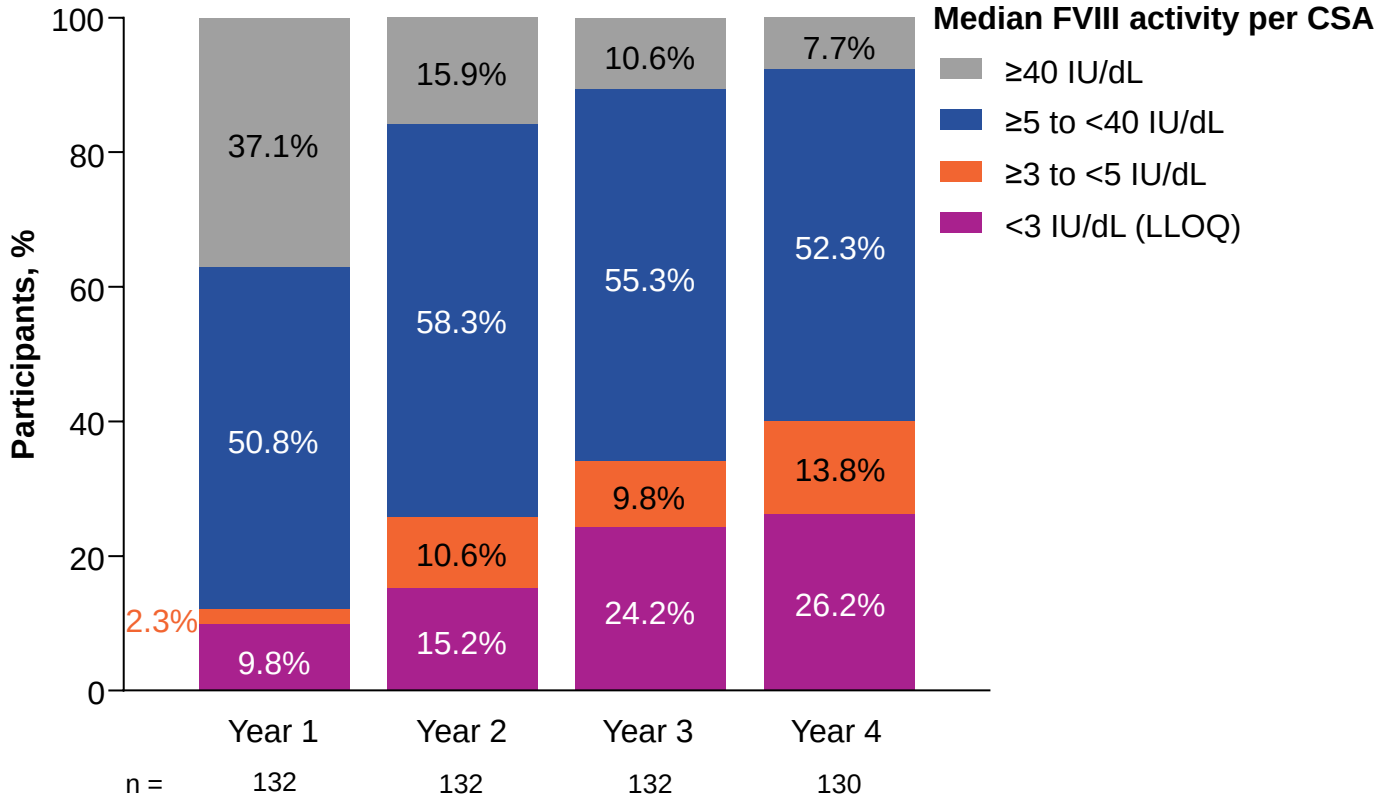
Because 2 participants did not reach year 4 follow-up, week 208 data are based on 130 participants. For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.

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

FVIII activity ranges at the end of year 4

mITT population *(chromogenic substrate assay)*

Most participants remain in the mild hemophilia range



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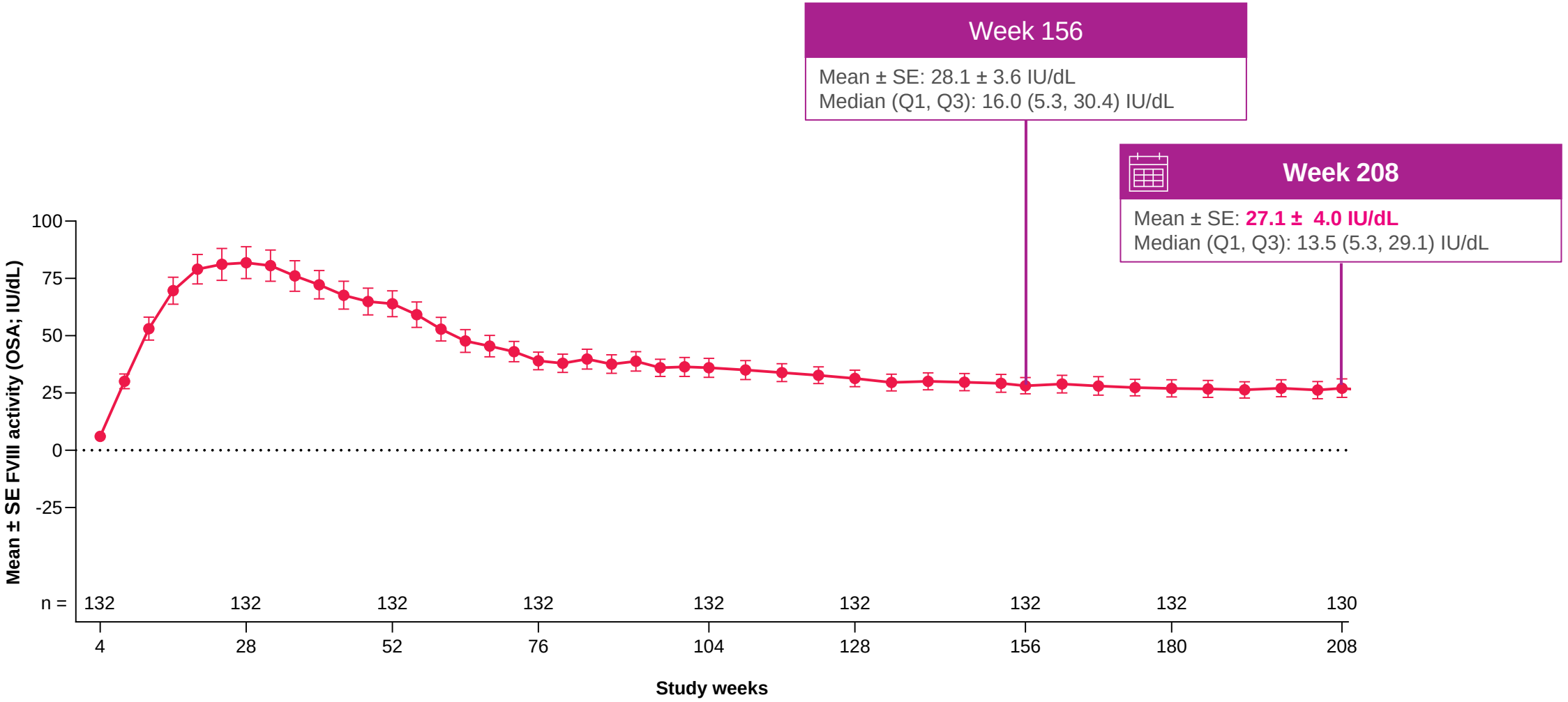
CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intent-to-treat.

FVIII activity between years 3 and 4

mITT population *(one-stage assay)*



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; mITT, modified intent-to-treat; OSA, one-stage assay; Q, quartile; SE, standard error.

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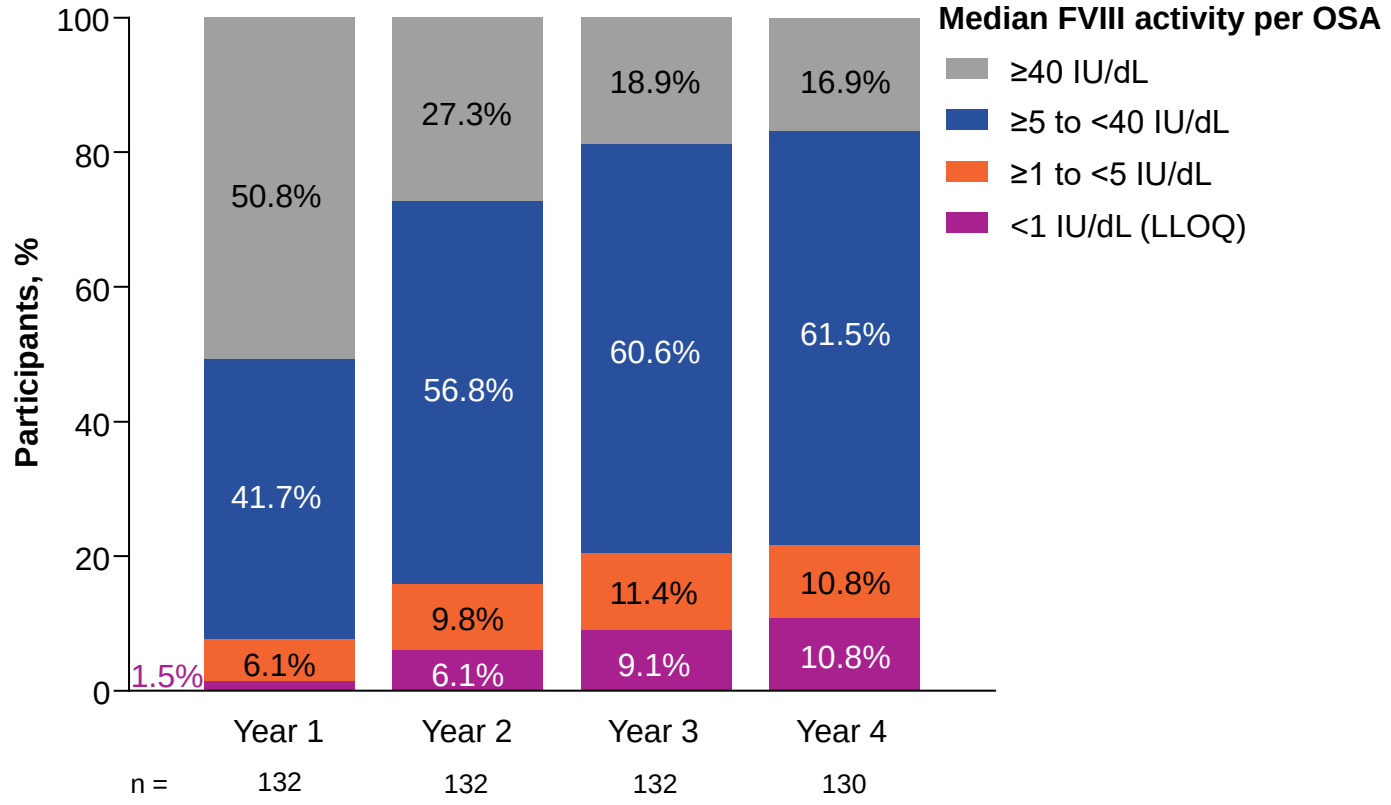
FVIII activity ranges at the end of year 4

mITT population *(one-stage assay)*

Most participants remain in the mild hemophilia range



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

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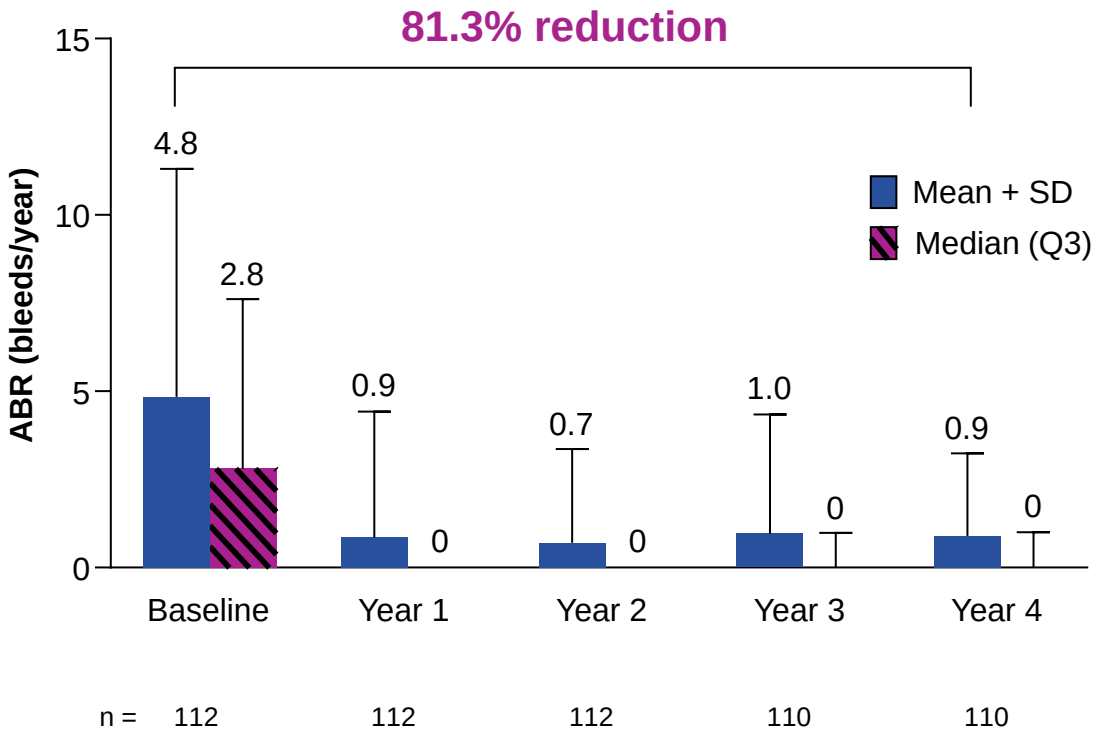
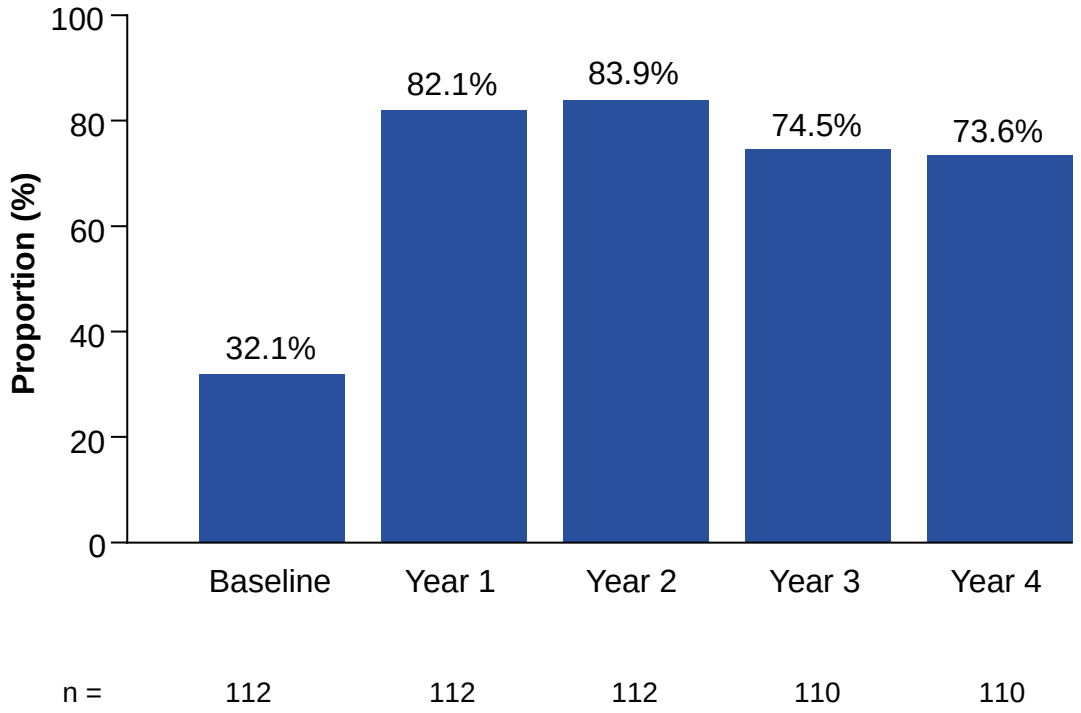
Reduction in treated bleeds maintained over 4 years

Rollover population

ABR for treated bleeds decreased >80% from baseline to year 4



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

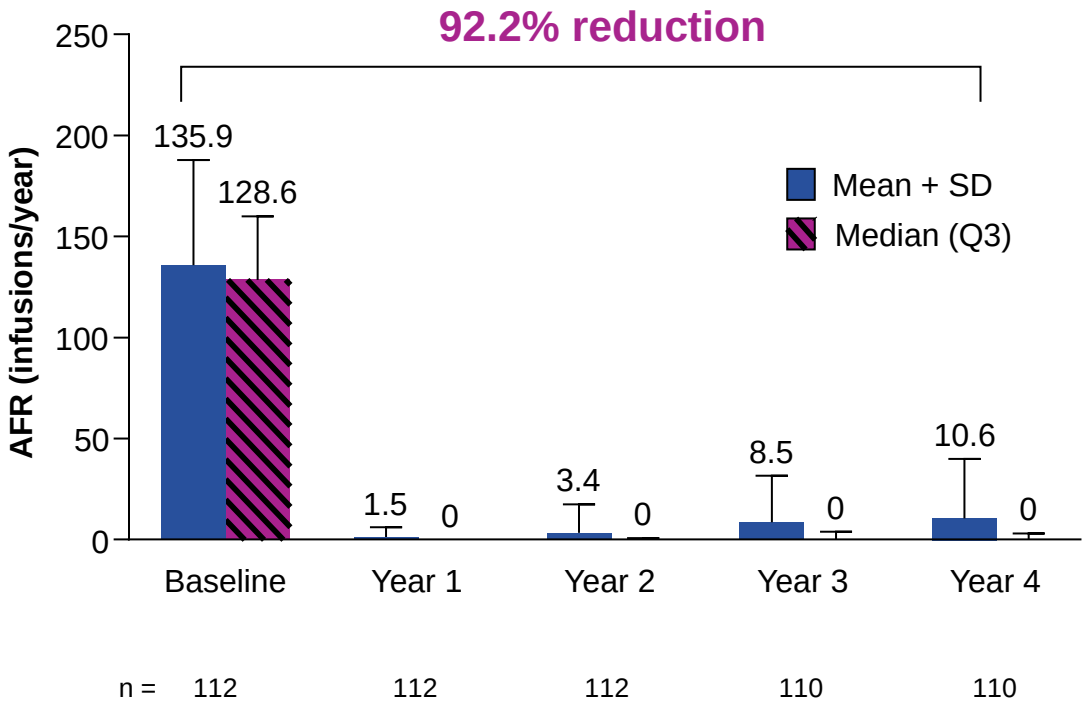


Missing data were not imputed.
ABR, annualized bleeding rate; Q, quartile; SD, standard deviation.

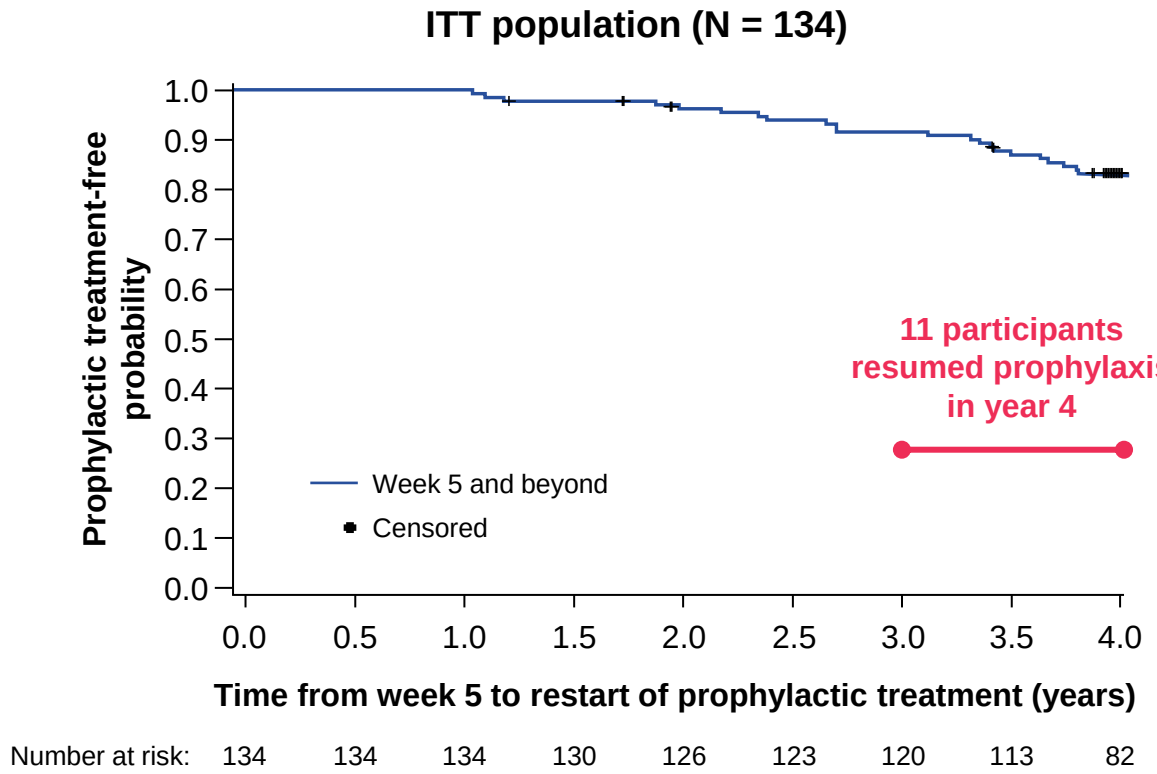
Reduction of FVIII infusion rate maintained through year 4

Rollover population

Annualized FVIII infusion rate decreased >90% from baseline to year 4



Over 4 years, 22 participants resumed prophylaxis



Missing data were not imputed.

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

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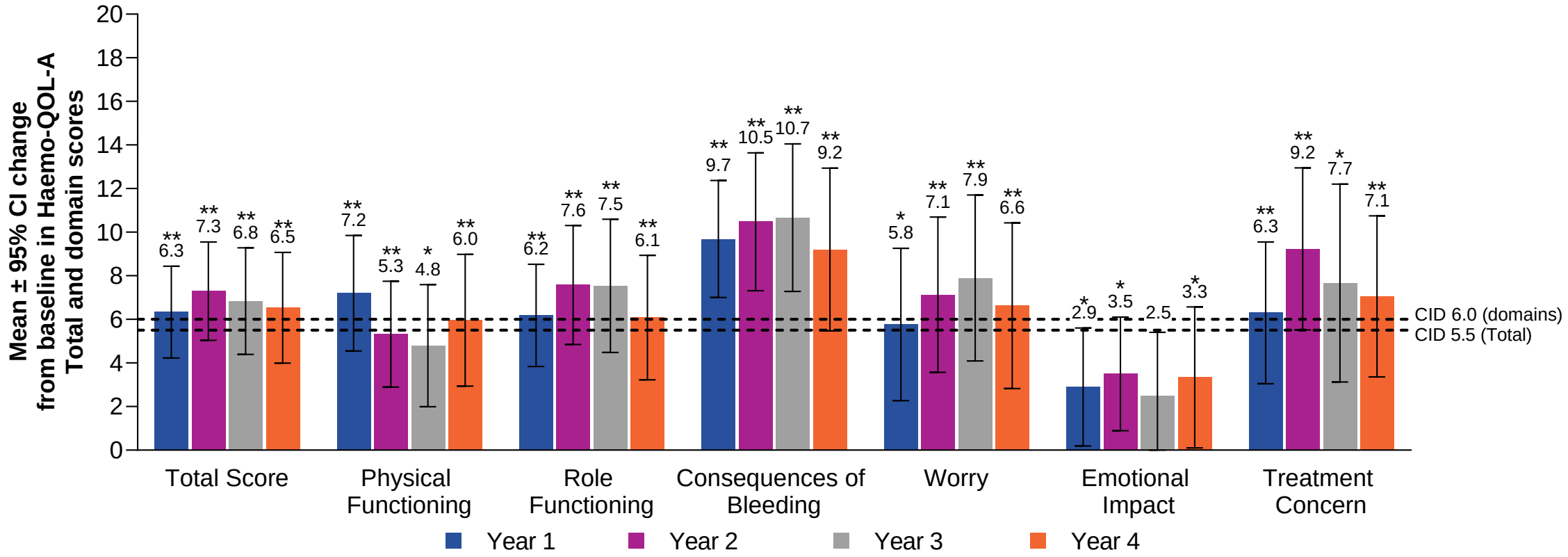
Haemo-QOL-A improvement maintained after 4 years

mITT population

Haemo-QOL-A Total Score increased 6.5 points from baseline, exceeding the CID of 5.5[1]



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

**P* <0.05, ***P* <0.001. Haemo-QOL-A Total Score change from baseline results are based on available data at each time point. Data were excluded after participants resumed prophylaxis.

CI, confidence interval; CID, clinically important difference; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; mITT, modified intent-to-treat.

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Conclusions

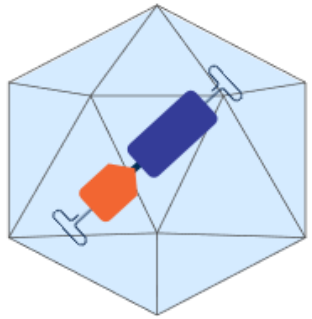
After 4 years, a single infusion of valoctocogene roxaparvovec provided durable bleeding protection and improved HRQOL with an acceptable safety profile

No new safety signals

- ALT elevation remained the most common AE in year 4
- No glucocorticoids were used for ALT elevations in year 4
- 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



Durable hemostatic efficacy

- Rate of treated bleeds during year 4 remains decreased >80% from baseline
- Most participants had no treated bleeds during year 4

Maintained improvements in HRQOL

- Clinically relevant improvements in Haemo-QOL-A Total Score were maintained at the end of year 4

1. Mahlangu J, et al. *N Engl J Med*. 2023;388:694-705.

AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; HRQOL, health-related quality of life; Y, year.

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